ARVO
The Association for Research in Vision and Ophthalmology

IT-ARVO Chapter Meeting

The Eye Clinic
Polytechnic University of Marche
Head: Prof Alfonso Giovannini

The role of TNF-α in uveitis: from pathophysiology to treatment

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The Copernican Revolution in Pharmacology

Therapeutic breakthroughs

1930-40	1950	1960	1988	1995	1998+
Gold salts Sulfasalazine Hydroxychloro-quine	Glucocor-ticoids	NSAIDs Penicillamine	Methotrexate (MTX)	Combo therapy	Anti-TNF Biologics

Biologics


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Biologics

- Biologics: drugs created by biologic processes, rather than being chemically synthesized.
- Different types:
  - Monoclonal Antibodies
  - Fusion Proteins
  - Other (i.e.: Interferon)


Who is the Killer?

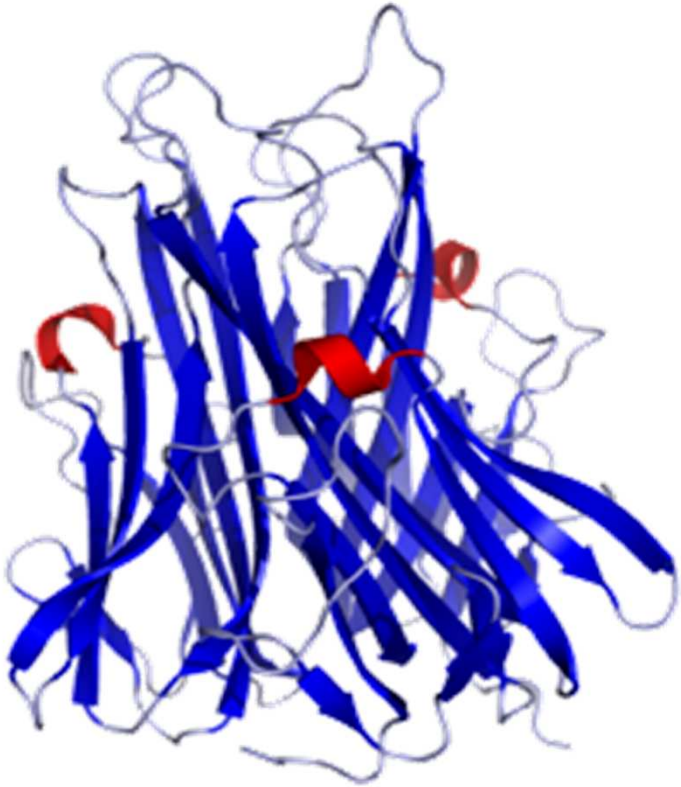
Table. 1 List of the most relevant biologic agents used in ophthalmology.

Name/Commercial name	Indications	Technology	Mechanism of action
Adalimumab/Humira	rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease	monoclonal antibody	TNF antagonist
Infliximab/Remicade	rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease	monoclonal antibody	TNF antagonist
Anakinra/Kineret	rheumatoid arthritis	recombinant human interleukin-1 receptor antagonist	Interleukin-1 receptor binder
Daclizumab/Zenapax	prevention of renal transplant rejection	monoclonal antibody	Interleukin-2 receptor binder
Abatacept/Orencia	rheumatoid arthritis	immunoglobulin CTLA-4 fusion protein	T-cell deactivation
Rituximab/ MabThera	CD20-positive non-Hodgkins lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis	monoclonal antibody	CD20 antigen binder
Alemtuzumab/ Campath-1H	B-cell chronic lymphocytic leukemia (B-CLL)	monoclonal antibody	CD52 antigen binder

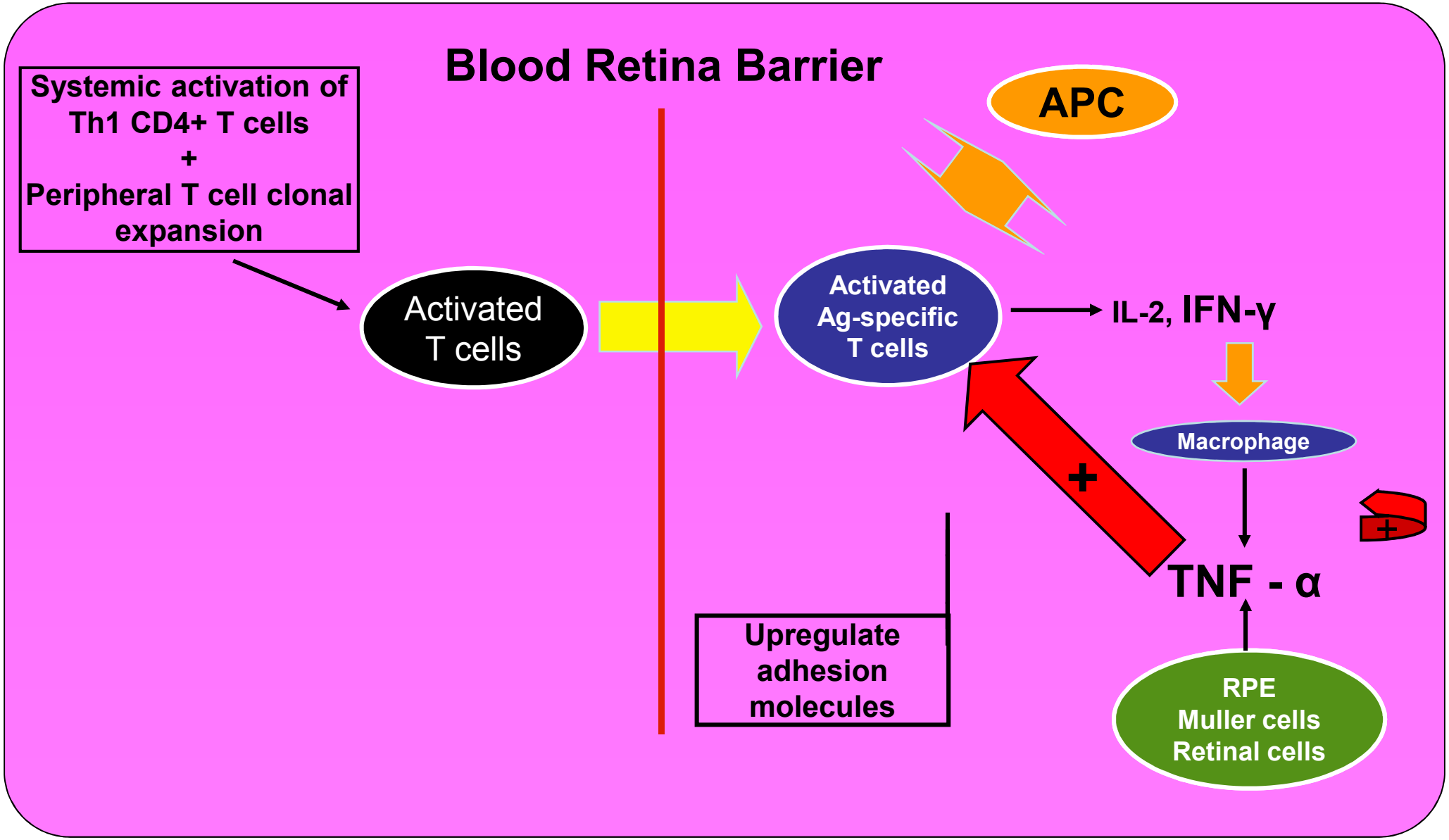
Posarelli C, Arapi I, Michele Figus M, Neri P 2011

Tumor Necrosis Factor-α

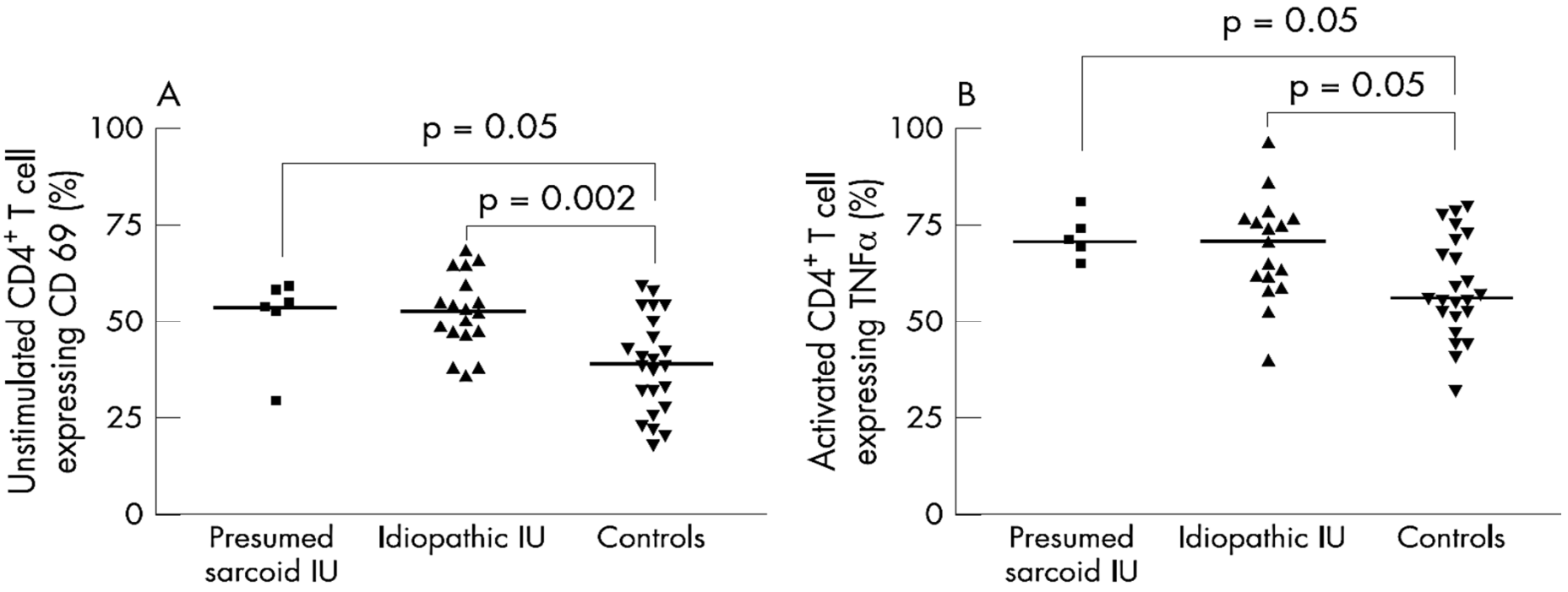
- Tumor necrosis factor (TNF, cachexin or cachectin and formally known as tumor necrosis factor-alpha) is a *cytokine* (tumor necrosis factors) involved in systemic inflammation and is a member of a group of cytokines that all stimulate the acute phase reaction
- TNF causes apoptotic cell death, cellular proliferation, differentiation, inflammation, tumorigenesis, and viral replication
- *TNF's primary role is in the regulation of immune cells*



Role of CD4+ T Cells and TNF-α in EAU

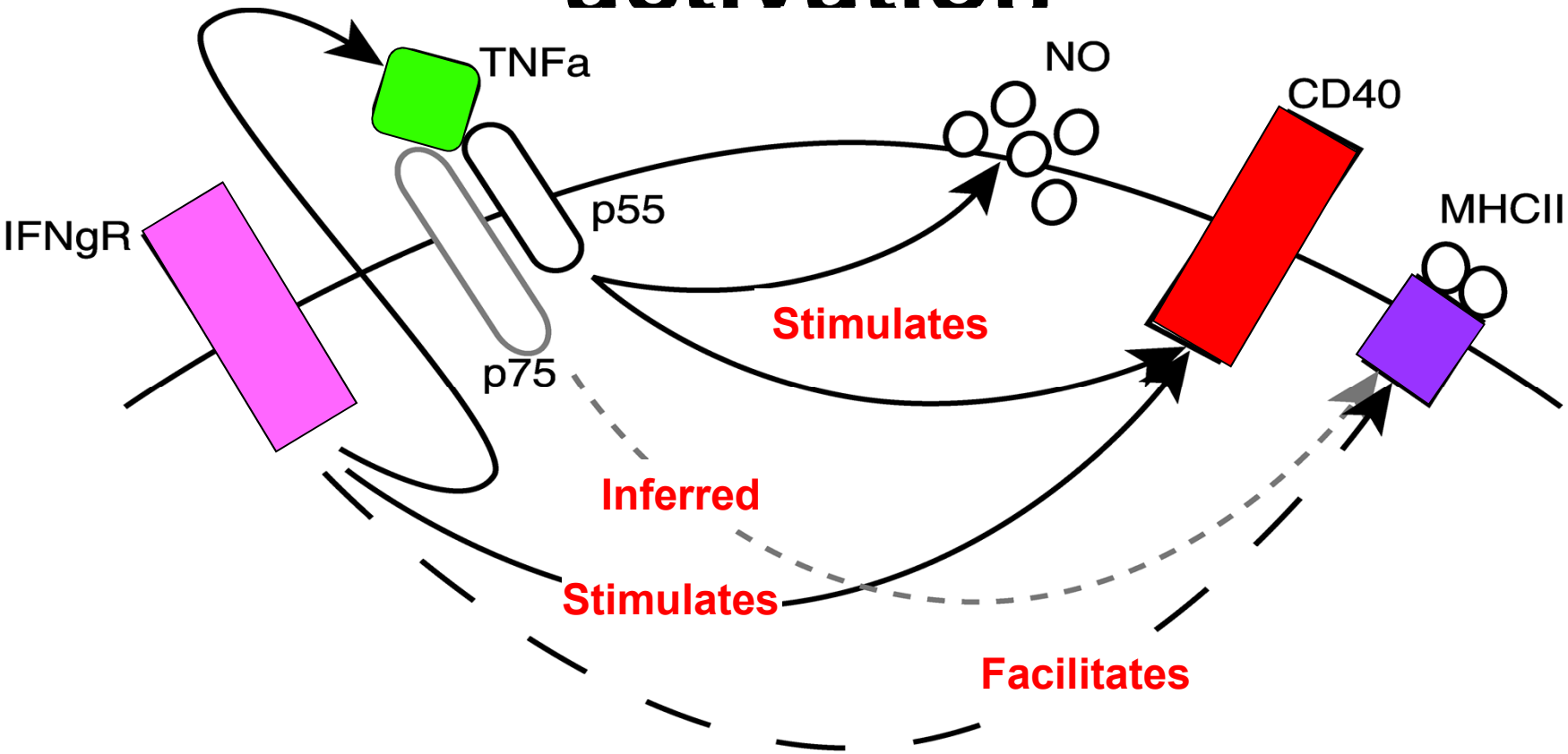


T cell activation and TNF production in intermediate uveitis



Murphy CC, et al. Br J Ophthalmol 2004;88:412–416

Regulation of macrophage activation

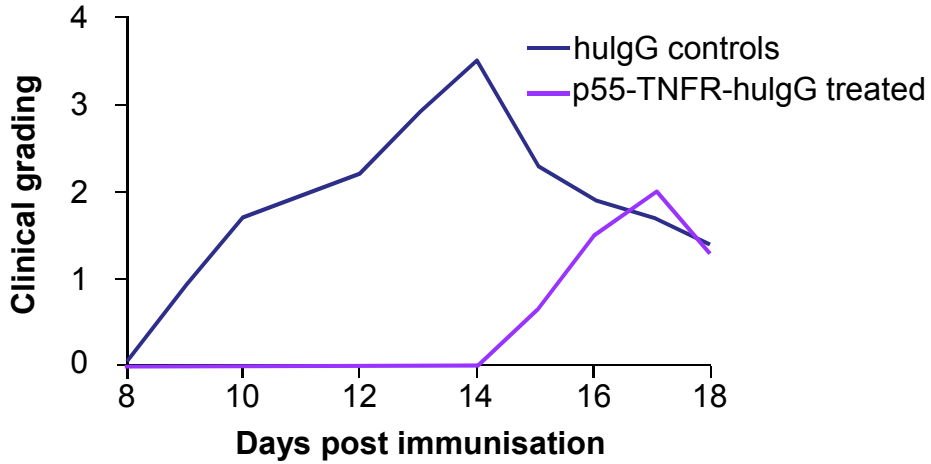


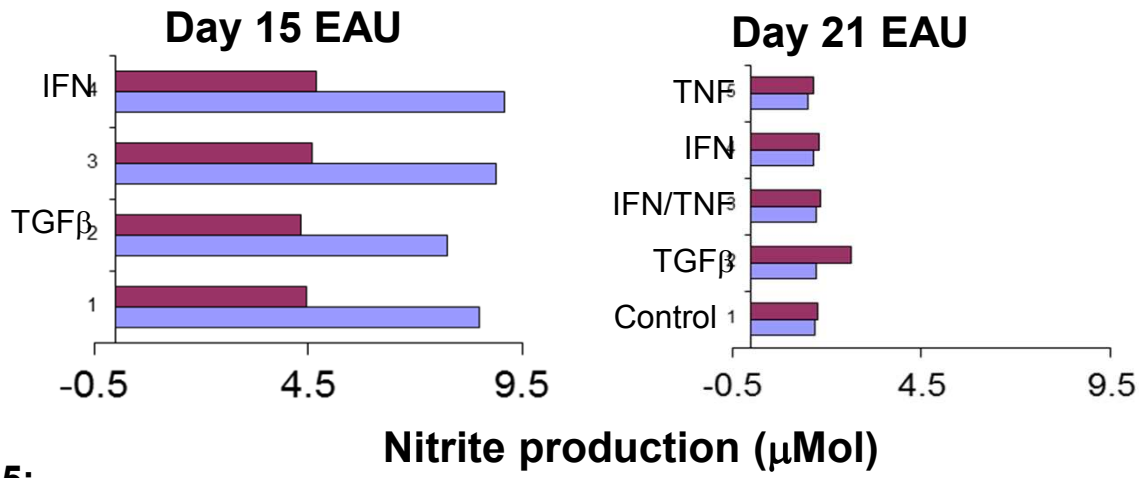
Adapted from Calder CJ, et al. J Immunol 2005;175:6286–6293

Neutralising TNF activity reduces tissue damage

Therapy with fusion protein of p55TNFr:

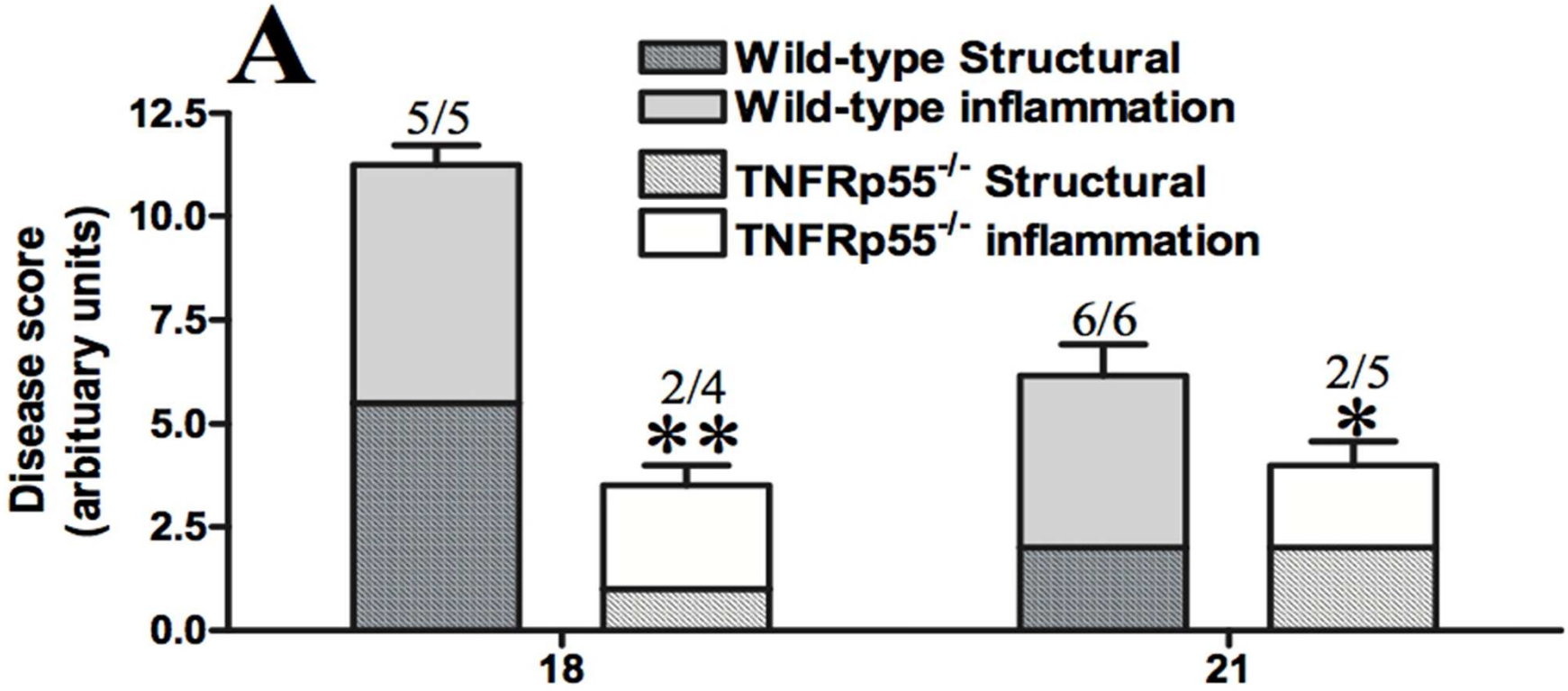
- Suppresses target organ damage despite continued leukocytic infiltrate
- Suppresses Th1 response
- Suppresses apoptosis of T cells in retina
- Down regulates macrophage activity





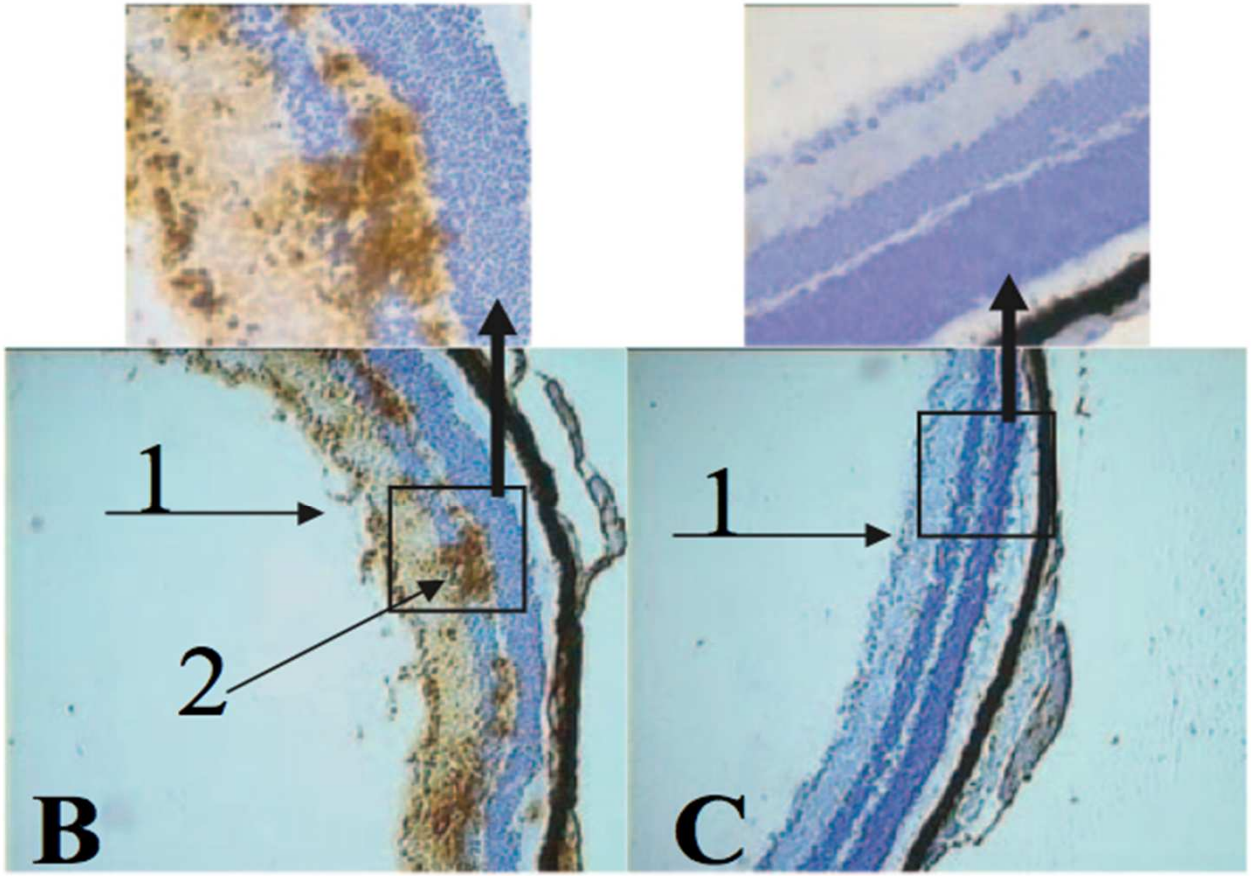
Dick AD, et al. Eur J Immunol 1996;26:1018–1025;
Dick AD, et al. J Autoimmun 1998;11:255–264

EAU in TNF p55 receptor deficient mice



Calder CJ, et al. J Immunol 2005;175:6286–6293

EAU in TNF p55 receptor deficient mice



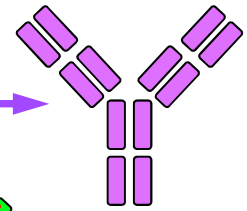
WT TNFRp55$^{-/-}$

Calder CJ, et al. J Immunol 2005;175:6286–6293

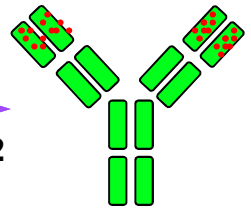
Evolution of Antibody

Golimumab (Simponi) 2009

Transgenic human mAb‘s
1994 Lonberg et al.; 1994 Green et al.

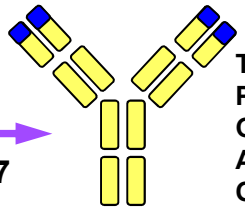


Phage Display synthetic mAb‘s
1990 McCafferty



Adalimumab (Humira) **2002**

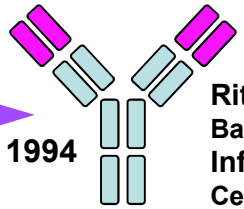
CDR0-modified mAb‘s
1986 Jones et al.



Daclizumab(Zenapax) **1997**

Trastuzumab (Herceptin)
Palivizumab (Synagis)
Gemtuzumab (Mylotarg)
Alemtuzumab (Campath)
Omalizumab (Xolair)
Efalizumab (Raptiva)
Bevacizumab (Avastin)

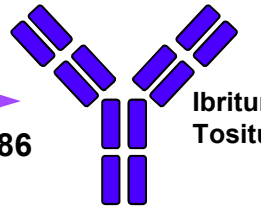
Chimeric recombinant mAb‘s
1984 Morrison et al.



Abciximab (RheoPro) **1994**

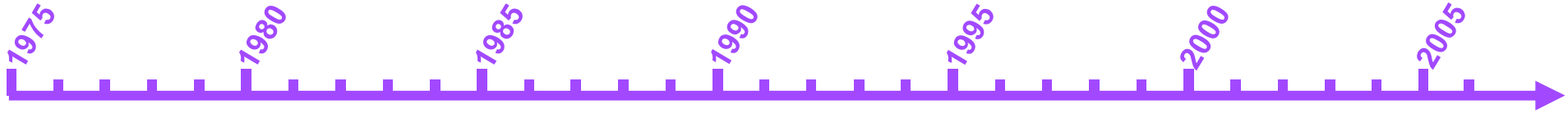
Rituximab (Rituxan)
Basiliximab (Simulect)
Infliximab (Remicade)
Cetuximab (Erbitux)

Murine monoclonal Ab‘s (mAb’s)
1975 Koehler & Milstein



Muromonab-CD3 (Orthoclone OKT3) 1986

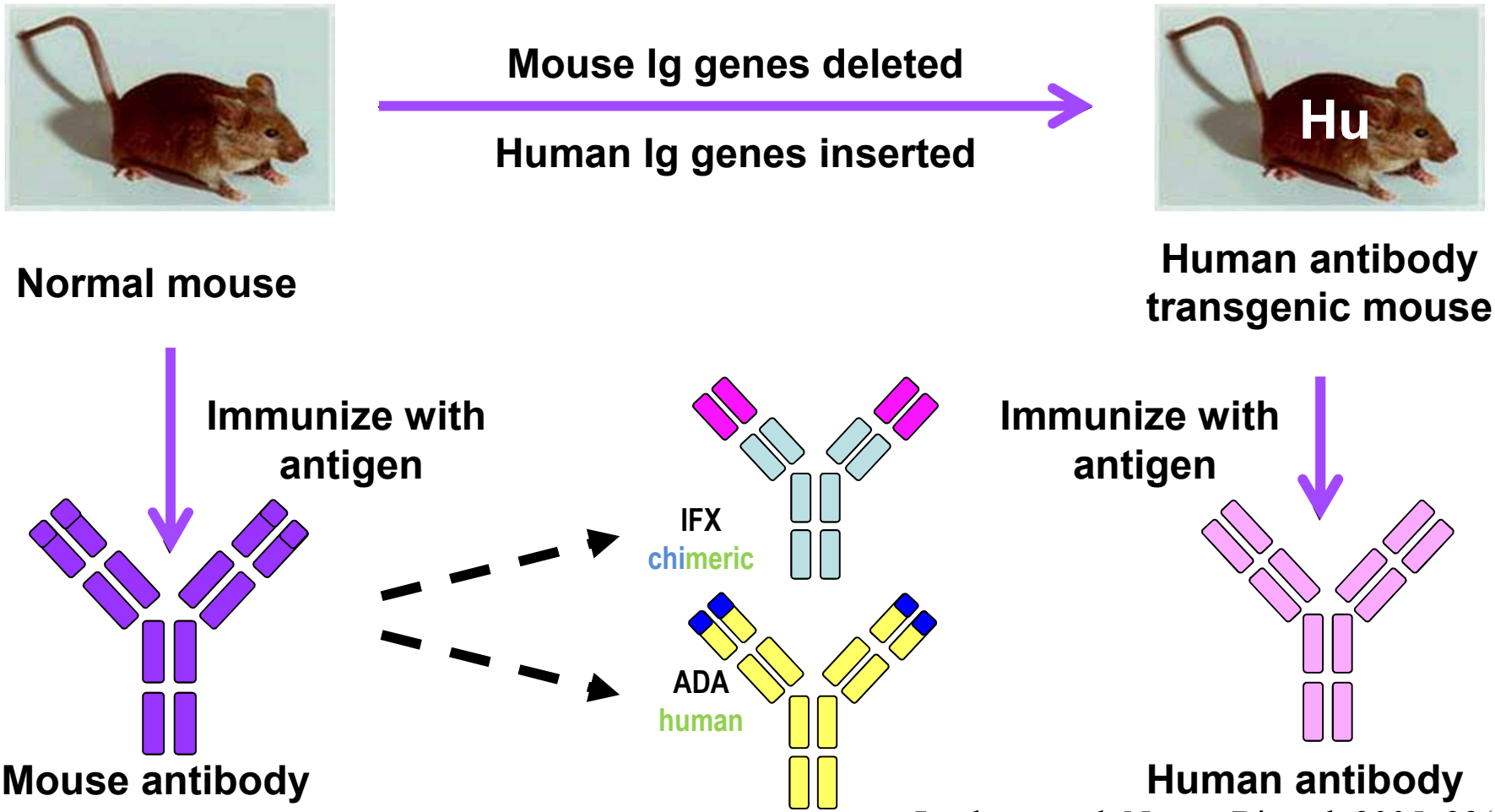
Ibritumomab (Zevalin)
Tositumomab (Bexxar)



*** adapted from: Nils Lonberg: Human antibodies from transgenic animals; Nat. Biotech. Sep 2005. Vol 23 No 9: 1117**

Development of Human Antibodies Using Human Antibody Transgenic Mice

For clarity, several intermediate steps are not shown.



Lonberg et al. Nature Biotech 2005; 23(9): 1117

http://www.medarex.com/Development/Evolution.htm

EXTENDED REPORT

Efficacy of tumour necrosis factor blockers in reducing uveitis flares in patients with spondylarthropathy: a retrospective study

S Guignard, L Gossec, C Salliot, A Ruyssen-Witrand, M Luc, M Duclos, M Dougados

Ann Rheum Dis 2006;**65**:1631–1634. doi: 10.1136/ard.2006.052092

See end of article for authors' affiliations

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Objective: To evaluate the efficacy of anti-tumour necrosis factor (TNF) treatments (given for rheumatological manifestations) in reducing uveitis flares in patients with spondylarthropathy in daily practice.

Methods: A retrospective observational study of all patients with spondylarthropathy with at least one uveitis flare treated with anti-TNF in one centre (December 1997–December 2004). The number of uveitis flares per 100 patient-years was compared before and during anti-TNF treatment; each patient was his or her own control. The relative risk (RR) and the number needed to treat (NNT) were calculated.

Results: 46 patients with spondylarthropathy treated with anti-TNF drugs had at least one uveitis flare (33 treated with anti-TNF antibodies, infliximab or adalimumab, and 13 with soluble TNF receptor, etanercept). The mean age at first symptoms was 26 years, 71% were men. Patients were followed for 15.2 years (mean) before anti-TNF versus 1.2 years during anti-TNF treatment. The number of uveitis flares per 100 patient-years before and during anti-TNF were, respectively: for all anti-TNF treatments,—51.8 *v* 21.4 ($p = 0.03$), RR = 2.4, NNT = 3 (95% confidence interval (CI) 2 to 5); for soluble TNF receptor—54.6 *v* 58.5 ($p = 0.92$), RR = 0.9; and for anti-TNF antibodies—50.6 *v* 6.8 ($p = 0.001$), RR = 7.4, NNT = 2 (95% CI 2 to 5).

Conclusion: Anti-TNF treatments were efficacious in decreasing the number of uveitis flares in patients with spondylarthropathy. Anti-TNF antibodies decreased the rate of uveitis flares, whereas soluble TNF receptor did not seem to decrease this rate. These results could have consequences for the choice of anti-TNF treatment in certain patients.

Table 2 Uveitis flares before and during each kind of anti-tumour necrosis factor (TNF) treatment (n = 46 patients), in patients with spondylarthropathy; comparison between uveitis flares during the treatment with those during treatment with the soluble TNF receptor

Anti-TNF (n = patients)	Pre-treatment period (years) Mean (SD)	Pre-treatment uveitis flares/ patient Mean (SD)	Pre-treatment uveitis flares/100 patient-years Mean (SD)	Treatment period (years) Mean (SD)	Number of uveitis flares/ patient Mean (SD)	Number of uveitis flares/100 patient-years Mean (SD)	p Value*
All anti-TNF n = 46	15.2 (10.2)	6.3 (9.7)	51.8 (65.0)	1.2 (1.1)	0.2 (1.0)	21.4 (74.9)	0.03
Soluble TNF receptor (etanercept) n = 13	11.5 (10.4)	3.6 (4.1)	54.6 (78.2)	1.2 (1.1)	0.5 (0.8)	58.5 (121.9)	0.92
Anti-TNF antibodies (adalimumab and infliximab) n = 33	16.7 (9.8)	7.3 (11.1)	50.6 (61.0)	1.2 (1.1)	0.1 (1.0)	6.8 (39.3)	0.001
Infliximab n = 25	16.8 (10.4)	7.3 (12.1)	47.4 (58.9)	1.4 (1.3)	0.2 (1.2)	9.0 (45.2)	0.008
Adalimumab n = 8	16.2 (8.7)	7.2 (7.8)	60.5 (70.4)	0.6 (0.2)	0	0	0.04

TNF, tumour necrosis factor.
*p Value comparing the number of uveitis flares/100 patient-years before and during the treatment. Each patient is his or her own control.


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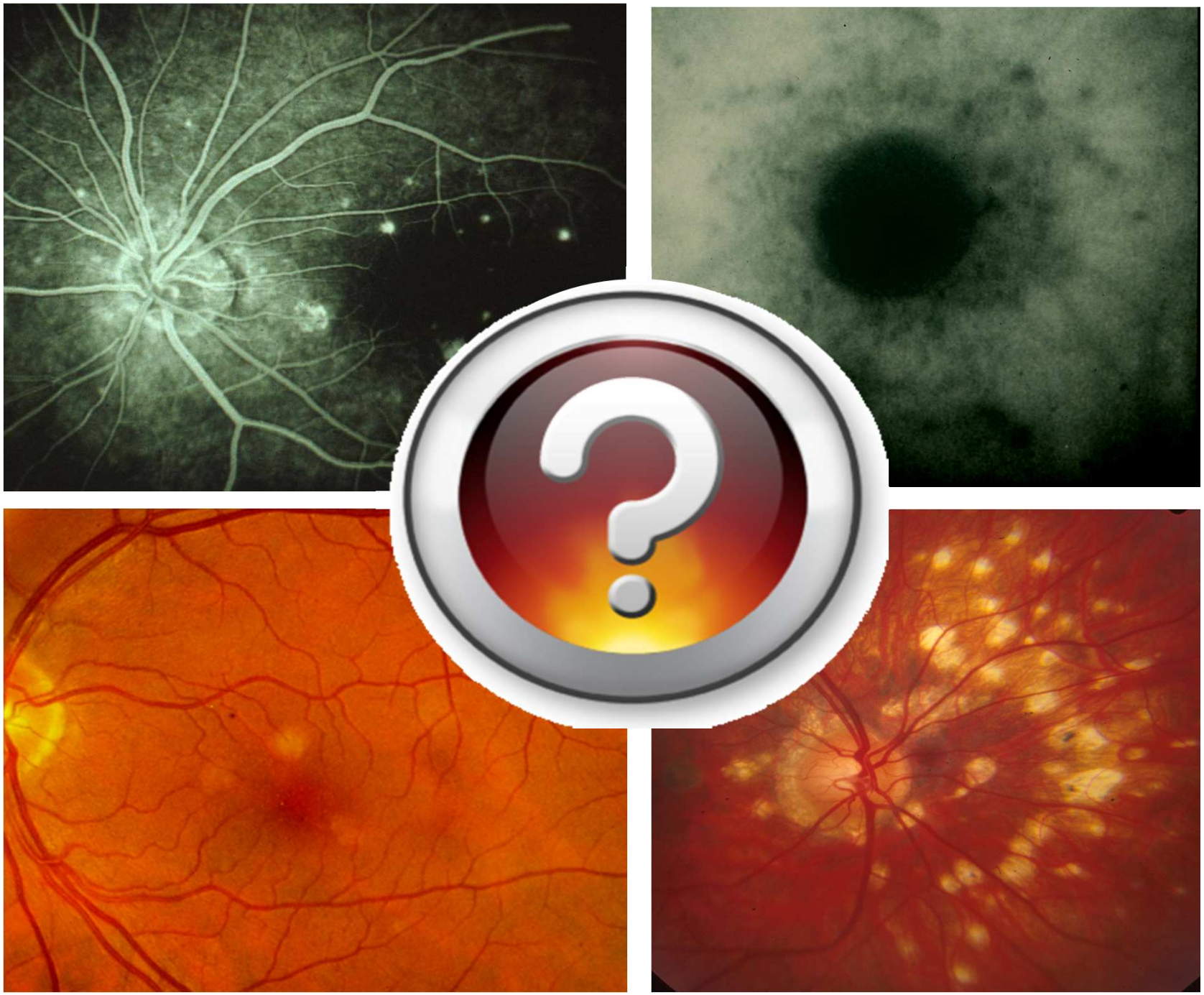



HELP!!!!!!

When anti-TNF-α Identikit

Uveitis

- Non-responder
- Severe
- Steroid dependant
- Traditional immunesuppressives not effective

When ophthalmologist stands alone

Financial Issues

Intravenous

+

=

Day Hospital

Sub-cutaneous

+

=

Domiciliary Care

Eye (2007) 21, 824–825

www.nature.com/eye

CASE SERIES

Adalimumab for sight-threatening uveitis in Behçet's disease

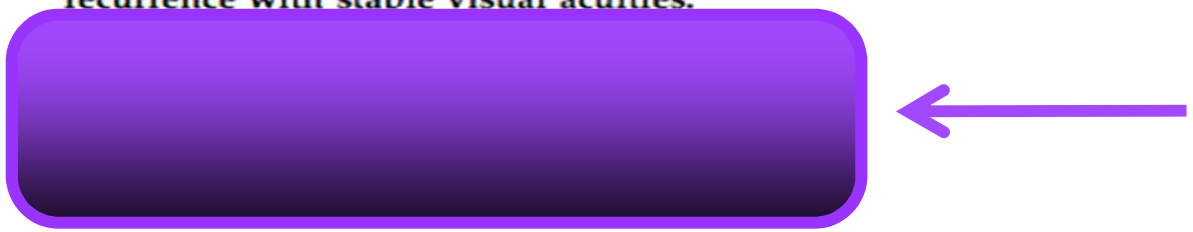
B Mushtaq[1], T Saeed[1], RD Situnayake[2] and PI Murray[1]

Abstract

Aims To describe the clinical outcome of three patients with Behçet's disease maintained on infliximab who were switched to adalimumab therapy.

Methods Case note review. Main outcome measure was recurrence of uveitis.

Results All patients remained free of recurrence with stable visual acuities.



Keywords: uveitis; Behçet's disease; therapy; adalimumab

	Previous treatment	***Motivation for treatment change***	***Before treatment***		***After treatment***		***Current treatment***	***Follow-up***
			RE	***LE***	***RE***	***LE***		
Case 1	i.v. and oral steroids, CSA, MTX, CYP,Infliximab	Difficulty to attend hospital for the i.v. infusions	6/9	6/18	6/9	6/18	Humira	2ys
Case 2	i.v. and oral steroids, CSA, AZA, MTX, CYP,Infliximab	Difficulty to attend hospital for the i.v. infusions	HM	6/9	HM	6/9	Humira	3ys
Case 3	i.v. and oral steroid, ciclosporin, methotrexate, azathioprine, mycophenolate mofetil, and i.v. cyclophosphamide	Difficulty to attend hospital for the i.v. infusions	CF	6/36	1/60	6/36	Humira	3ys

Mushtaq B et Al. Eye 2007

Clin Exp Rheumatol. 2011 Jul-Aug;29(4 Suppl 67):S93. **Efficacy of switching to adalimumab in a patient with refractory uveitis of Behçet's disease to infliximab.** Leccese P, Latanza L, D'Angelo S, Padula A, Olivieri I.

Clin Exp Rheumatol. 2011 Jul-Aug;29(4 Suppl 67):S54-7. **Efficacy of adalimumab in patients with Behçet's disease unsuccessfully treated with infliximab.** Olivieri I, Leccese P, D'Angelo S, Padula A, Nigro A, Palazzi C, Coniglio G, Latanza L.

Eye (2009) 23, 1868–1870

www.nature.com/eye

CASE SERIES

Switching biologic agents for uveitis

N Dhingra, J Morgan and AD Dick

Abstract

Purpose **To observe whether switching between biological agents helps to gain or maintain uveitis remission in cases with sight-threatening refractory uveitis.**

Methods **We reviewed the case notes of seven patients with refractory uveitis, who had switched between biological agents. The switch between biological agents (infliximab or adalimumab) was for gaining control of systemic symptoms, uveitis, or for the ease of administration.**

Results **There were three adults (one each with sarcoidosis, ankylosing spondylites, and sero-negative polyarthropathy) and four children with juvenile idiopathic arthritis. The adults were switched twice between the various biological agents to gain adequate control of their systemic disease or to ease administration of the drug. All the children were switched to a second biological agent for gaining uveitis remission. Following the final switch, the concomitant immunosuppression in all the patients either reduced or remained unchanged, and only two patients remained on additional prednisolone (10 mg/day).**

Conclusions **Our case series provides preliminary evidence that in cases of refractory uveitis with loss of initial clinical response to one biological agent, switching to another agent can restore control of intraocular inflammation. In addition, switching helps to control systemic symptoms and allows ease of administration.**

Eye (2009) **23**, 1868–1870; doi:10.1038/eye.2009.203; published online 31 July 2009

Keywords: uveitis; biologics; infliximab; adalimumab

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Introduction

Since their discovery in the 1990s, biologic drugs[1] have been used to treat uveitis refractory to traditional immunosuppressants. Many questions on their use though have remained unanswered; particularly when to initiate therapy, which agent and at what dosage to use, and for how long the treatment should continue.[2] In the event of failure of desired response to one biologic therapy, the efficacy of switching from infliximab to adalimumab has been well described in other diseases, such as rheumatoid arthritis.[3] Switching between biologic agents has been done either for primary (poor response) or secondary failure (development of side effects or loss of effect secondary to human anti-chimera antibody development).[4] There is little evidence that switching between biologics helps to gain or maintain uveitis remission.

As part of an overall audit programme of immunomodulation for uveitis, we reviewed the case notes of seven patients with sight-threatening, refractory uveitis treated with biologic agents (Tables 1 and 2). Our series uses the standardised uveitis nomenclature (SUN)[5] grading system using the same outcomes to assess disease activity and measure efficacy as the ability to withdraw concomitant immunosuppression and/or reduction of prednisolone dose to below 10 mg/day. SUN grading refers to a standardised system in which AC cells are graded in a slit beam measuring 1×1 mm in size. The score is given as a number of cells in the field (0 < 1 cell, 0.5 + for 1–5 cells, 1 + for 6–15 cells, 2 + for 16–25 cells, 3 + for 26–50 cells and 4 + having >50 cells). The vitreous haze was graded using the National Eye Institute system using binocular indirect ophthalmoscope referred as BIO score,[6] where score 0 is given for absence of cells, 0.5 for presence of occasional cells, 1 where posterior pole is clearly visible, 2 for slightly hazy details, 3 for very hazy details, 4 for barely visible details, and 5 is where the details are not visible.

Case 1

Patient 1 had sarcoid-related uveitis with bilateral disc oedema and choroidal neovascularisation necessitating alemtuzumab

Table 1 Patient profile and switch agent used

Pt	*Sex*	*Age at presentation*	*Diagnosis*	*1st drug*	*Reason for switch*	*2nd drug*	*Reason for switch*	*3rd drug*
1	F	46	Sarcoidosis	Alemtuzumab	Persistent uveitis	Infliximab	Difficult venous access	[redacted]
2	F	33	A spondylites	Infliximab	Side effects	[redacted]	Persistent uveitis	Infliximab
3	F	4	JIA	Infliximab	Psoriasis flare-up		Worsening of joints	Infliximab
4	M	5	JIA	Infliximab	Persistent uveitis			
5	F	2	JIA	Infliximab	Persistent uveitis			
6	F	5	JIA	Infliximab	Persistent uveitis			
7	F	13	Idiopathic	Infliximab	Persistent uveitis			

Abbreviations: AC, anterior chamber; BIO, bioscore; JIA, juvenile idiopathic arthritis; VA, visual acuity (Log Mar); RE, right eye; LE, left eye; BE, both eyes; NA, patient did not have second switch; phaco, phacoemulsification of lens; vity, vitrectomy; PDT, photodynamic therapy; MTX, methotrexate; MMF, mycophenolate mofetil; Tac, tacrolimus; pred, prednisolone; Concom IMT, concomitant immunomodulation therapy.

6/7 Humira

Table 2 Patient disease activity with biologic switch agent

Pt	*Initial VA*	*Final VA*	*AC grade*				*BIO Score*				*Additional events*	*Concom IMT*				*Last Biologic (m)*
	RE, LE	*RE, LE*	*Initial*	*1st switch*	*2nd switch*	*Final*	*Initial*	*1st switch*	*2nd switch*	*Final*		*Initial*	*1st switch*	*2nd switch*	*Final*	
1	1.0, 1.60	0.8, 0.8	0, 0	0, 0	0.5, 0	0, 0	0.5, 0	0.5, 0	1, 1	0, 0	BE Phaco/vity, RE PDT	Tac, Pred (15 mg)	Tac, Pred (20 mg)	Tac, Pred (30 mg)	Tac, Pred (10 mg)	24
2	0.18, 0.18	0.18, 0.18	1, 0	0, 0	0.5, 0	0, 0	0, 0	0, 0	1, 1	0, 0	RE amblyopia	MTX	MTX	MTX	MTX	12
3	0.18, 0.30	0.18, 0.18	2, 1	1, 0	0, 0	1, 0	0, 0	NR	0, 0	0, 0	Post fossa medulloblastoma BE Phaco	MTX, Etan	MTX	MTX	MTX	9
4	0.0, 0.0	0.0, 0.0	0.5, 0.5	2, 3	NA	1, 1	0, 0	0, 0	NA	0, 0	—	MTX	MTX MMF		MMF	9
5	0.30, 0.48	0.0, 0.18	1, 1	1, 2	NA	0, 0	2, 1	0, 1	NA	0, 0	—	MTX	MTX		MTX	6
6	0.0, -0.10	0.0, -0.20	0.5, 0	0, 0	NA	1, 0	0, 0	0, 0	NA	0, 0	—	MMF MTX Pred (10 mg)	MMF, Pred (10 mg)		MMF	5
7	0.0, 0.60	0.0, 0.76	0, 0	0, 0	NA	0, 0.5	0, 0	1, 1	NA	0, 0	Chronic disc swelling	MMF Tac, Pred	MMF Pred (10 mg)		MMF Pred (7.5 mg)	6

Abbreviations: AC, anterior chamber; BIO, bioscore; JIA, juvenile idiopathic arthritis; VA, visual acuity (Log Mar); RE, right eye; LE, left eye; BE, both eyes; NA, patient did not have second switch; phaco, phacoemulsification of lens; vity, vitrectomy; PDT, photodynamic therapy; MTX, methotrexate; MMF, mycophenolate mofetil; Tac, tacrolimus; pred, prednisolone; Concom IMT, concomitant immunomodulation therapy.

Dhingra N et Al. Eye 2009

Review

Review Article

Adalimumab (Humira™) in Ophthalmology: A Review of the Literature

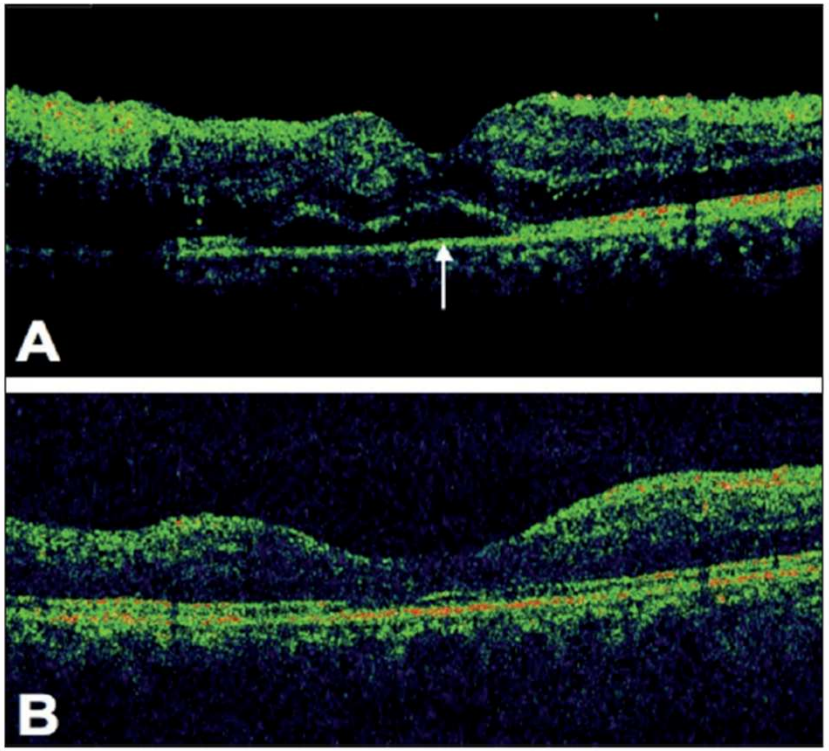
Piergiorgio Neri[1], Marta Lettieri[1,2], Cinzia Fortuna[1,2], Manuela Zucchi[1], Mara Manoni[1,2], Silvia Celani[1,2], Alfonso Giovannini[1,2]

ABSTRACT

Tumor Necrosis Factor alpha (TNF-α) is a pleiotropic cytokine which plays a primary role in the induction of inflammation in autoimmune diseases. The newest anti-TNF-α agent is adalimumab (Humira, Abbott Pharmaceutical Inc.), a human-derived antibody. This review summarizes the characteristics of adalimumab, highlighting its clinical use in systemic and ocular inflammatory disorders, and the possible therapeutic strategies. Adalimumab has been successfully used for the treatment of rheumatoid arthritis, ankylosing spondylitis, and psoriasis arthritis. More recently, adalimumab has shown promising qualities in controlling intraocular inflammations, even though this has been used prevalently as a rescue therapy for unresponsive cases. This biologic agent was also used in pediatric cases, showing a good safety and efficacy profile. Albeit no direct comparison with other biologics has been done, and adalimumab seems to be equivalent to the other anti-TNF-α, the switching to adalimumab can offer a better uveitic control. Adalimumab is a promising drug for the treatment of uveitis, even though further studies are needed on its application as a primary therapy in uveitis.

Key words: Adalimumab, Immunesuppression, Macular Edema, Uveitis, Vasculitis

DOI: 10.4103/0974-9233.71588

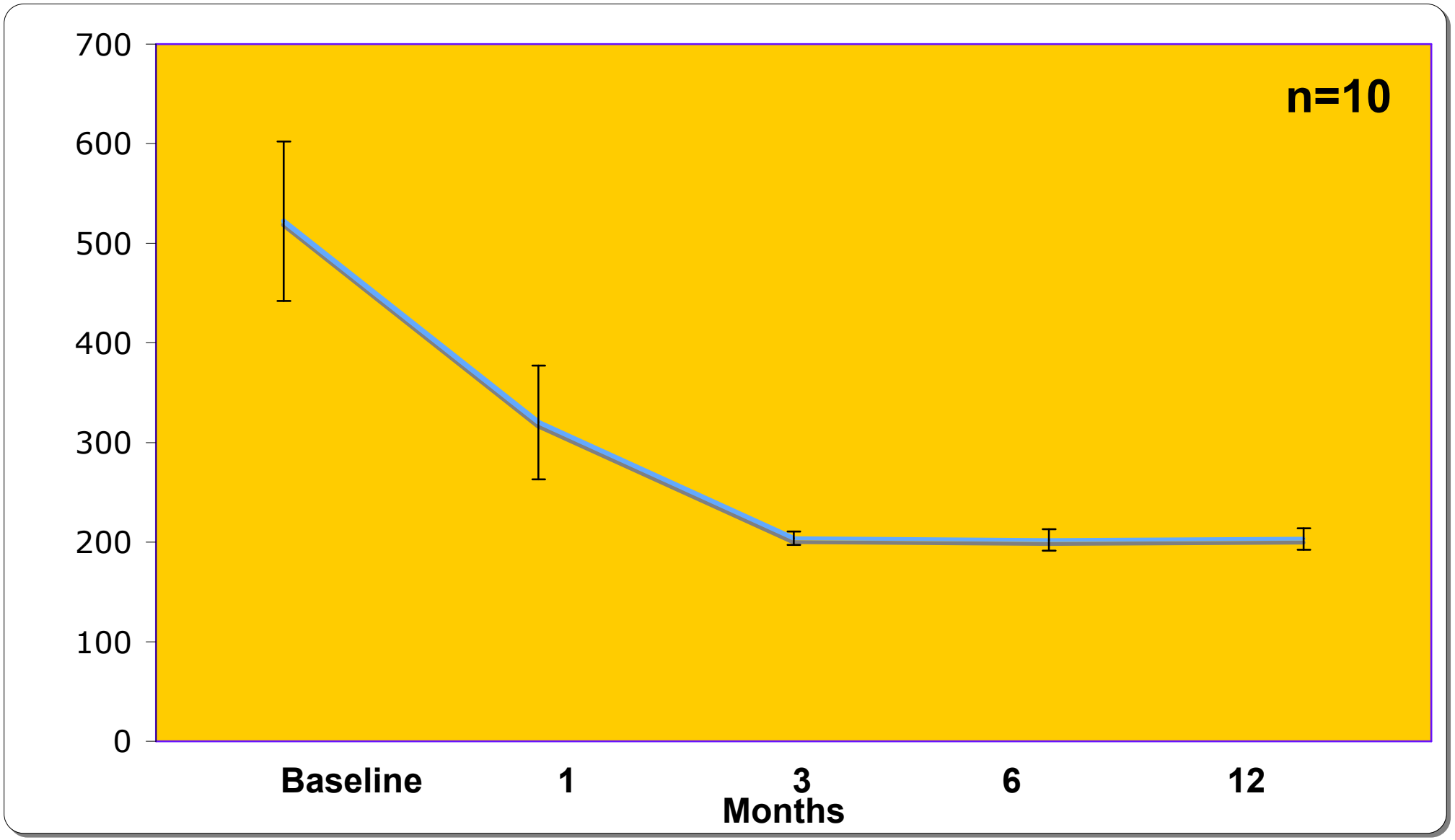


Summary

- Effective
- Safe (?)
- Promising

Neri P et Al. MEAJO 2010

Refractory Non-infectious Uveitis with CMO



Data on file 2009-2013

Long-term control of non-infectious paediatric panuveitis refractory to traditional immunesuppressive therapy successfully treated with Adalimumab (Humira™)

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Abstract

Objectives

The aim of this paper is to present two cases of severe idiopathic non-infectious paediatric panuveitis, unresponsive to traditional therapy, successfully treated with Adalimumab (Humira™, Abbott Pharmaceutical Inc.) in the long term.

Methods

The data of the two cases are presented and the literature is reviewed.

Results

At base line, case 1 had 0.2 in the RE and 0.5 in the LE, while case 2 had 0.5 and 0.4 in the RE and LE, respectively. The anterior chamber (AC) of case 1 had 3+ cells and 3+ flare in both eyes, as well as diffuse keratic precipitates (Kps). Case 2 presented 2+ cells and 3+ flare in both eyes, as well as tiny Kps in the inferior part of the endothelium. The Binocular Indirect Ophthalmoscopy (BIO) score was +2 in both eyes of case 1 and case 2 at first examination. After Adalimumab initiation, both patients presented a dramatic resolution of the ocular inflammation, as well as a rapid improvement of the BCVA. Case 1 had 0.8 and 1.0 in the RE and the LE, respectively, while case 2 presented 1.0 in both eyes. At the last visit, both patients presented a quiet uveitis and stable BCVA: case 1 had 0.8 and 1.0 in the RE and the LE, respectively, while case 2 presented 1.0 in both eyes. No side effects were recorded during this time.

Conclusion

Adalimumab can be a promising drug for the therapy of severe, refractory paediatric uveitis, although further studies are needed on its application in uveitis.

Key words

adalimumab, uveitis, immunesuppression, paediatric

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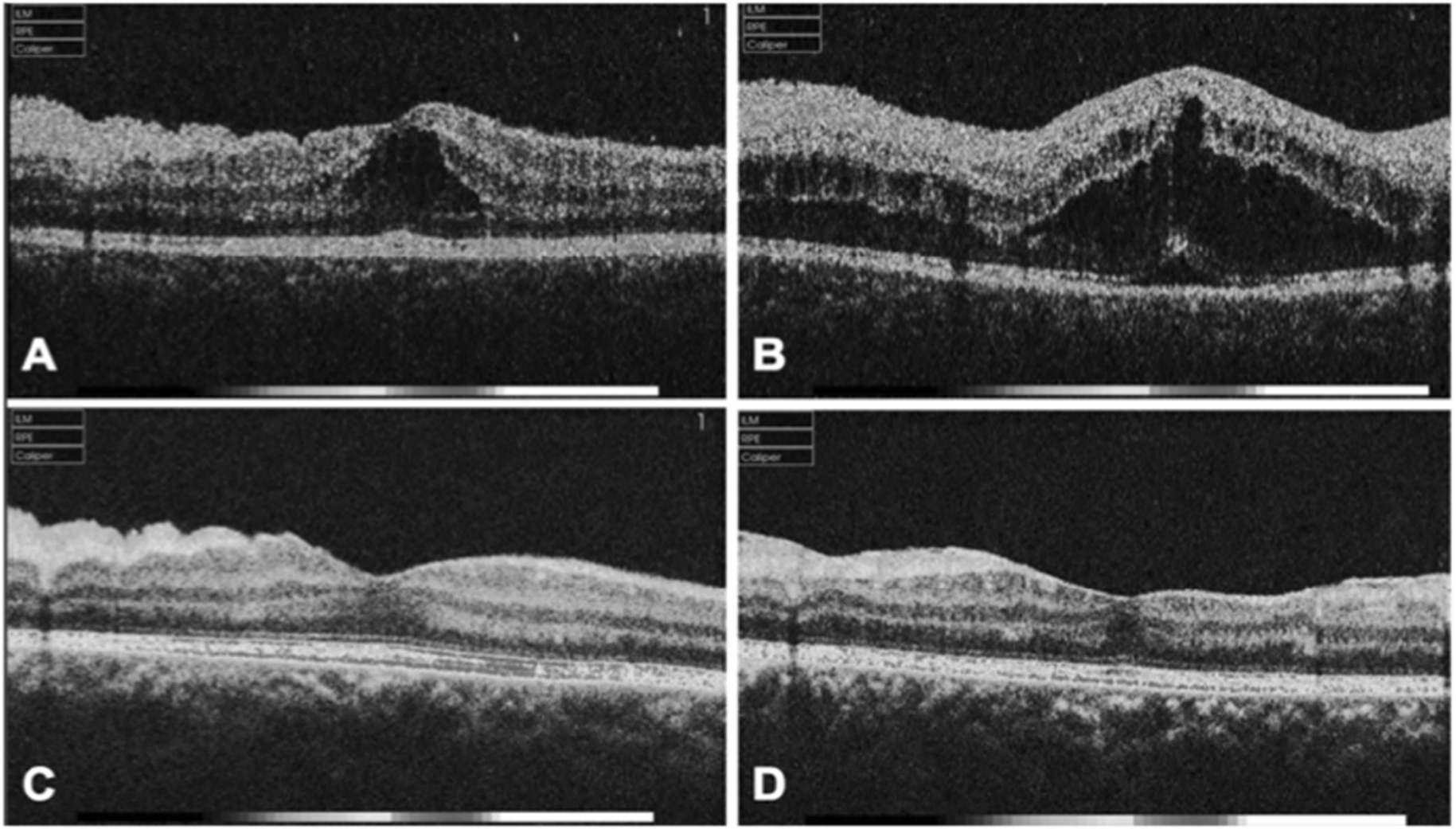

Fig. 1. Case 1: OCT showing intraretinal cysts (**A**), with an evident neurosensory detachment in the left eye (**B**). Note the resolution of the oedema after one month with Adalimumab therapy (**C** and **D**).

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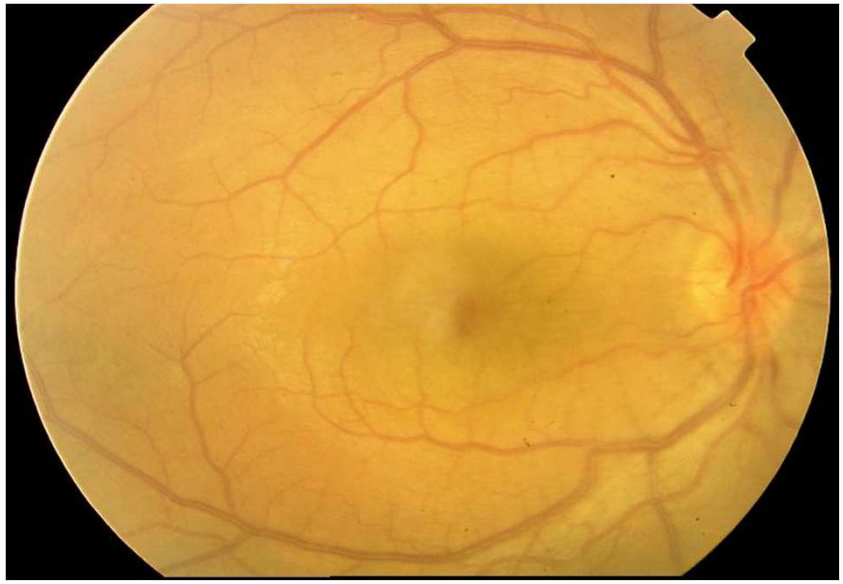
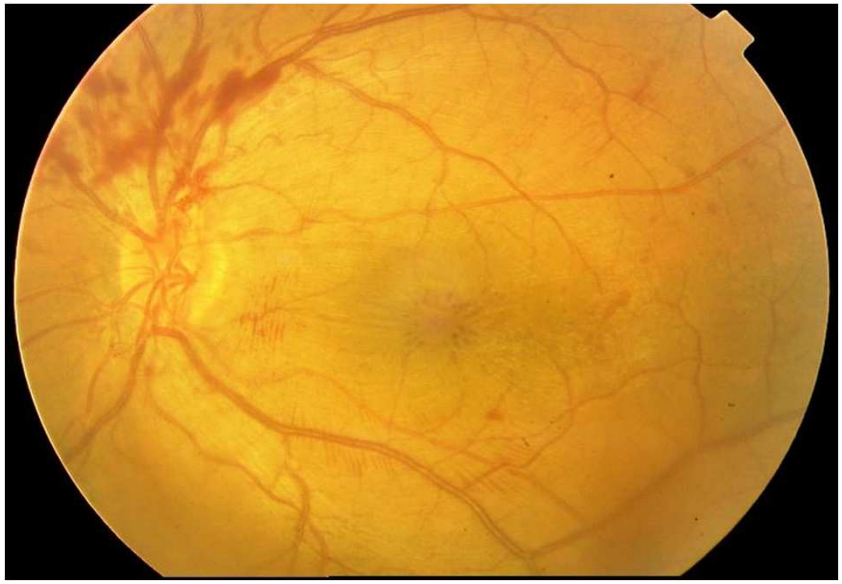
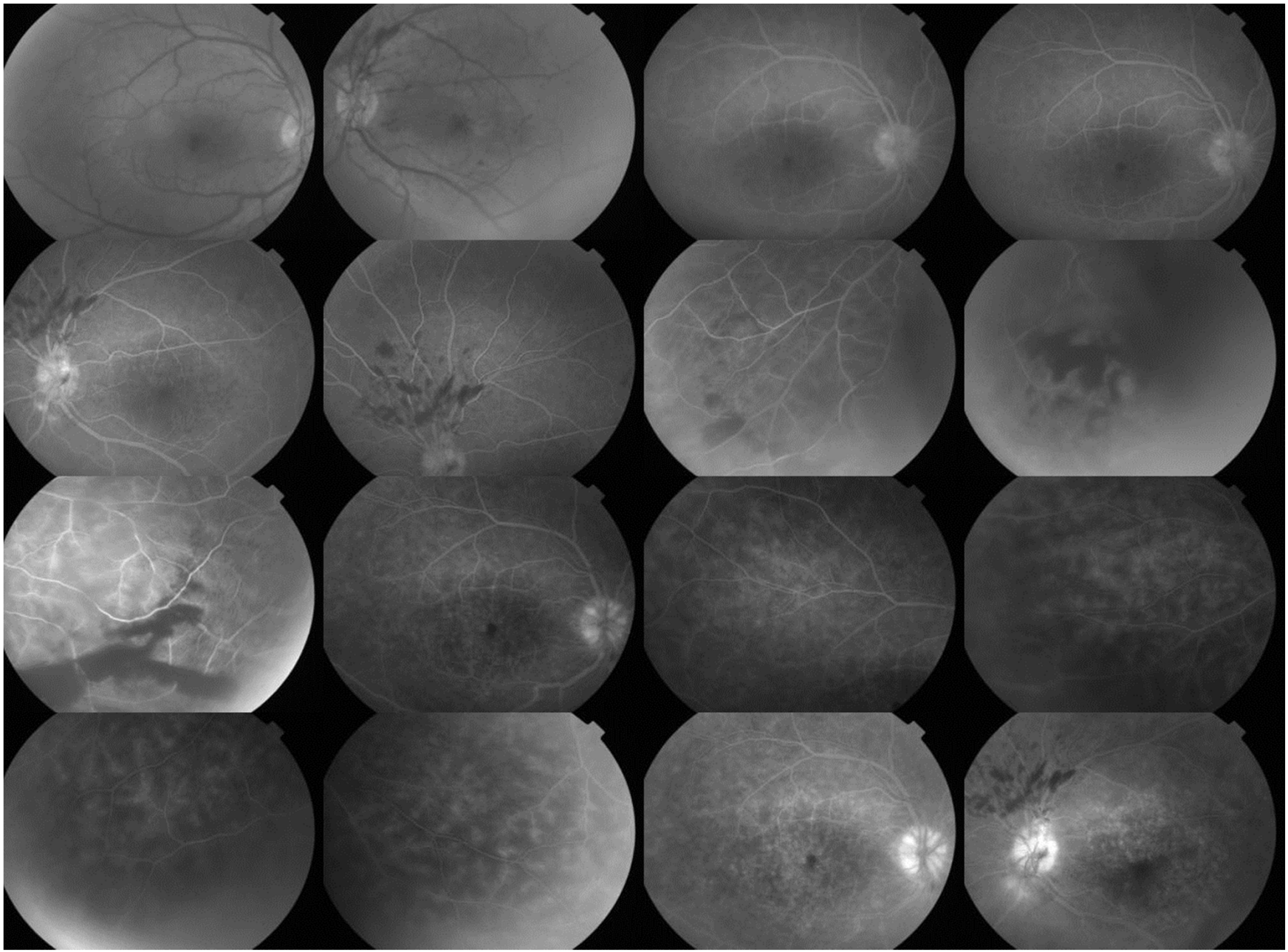
Selected case 1-Adalimumab



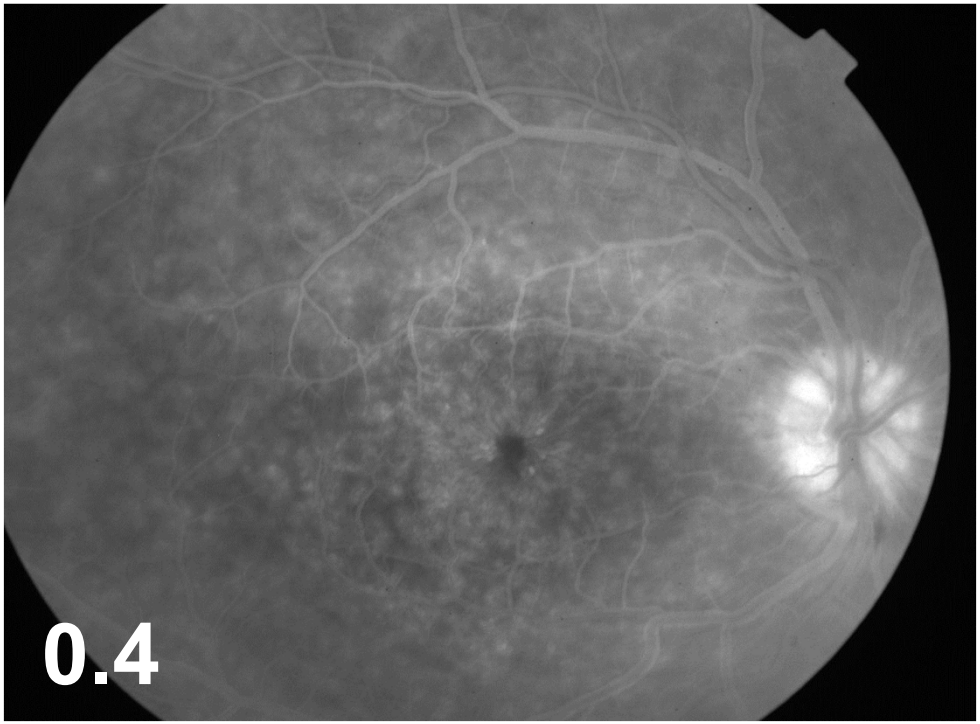


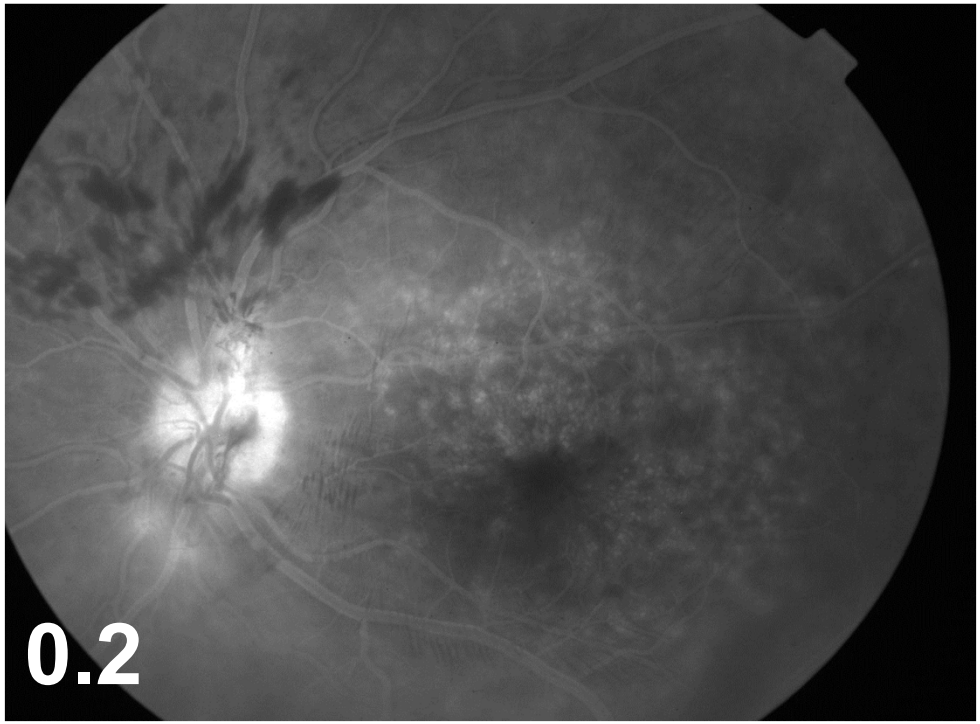
- Male
- 16-yr
- All tests negative
- Bilateral panuveitis with haemorrhagic retinal vasculitis
- Severe CMO

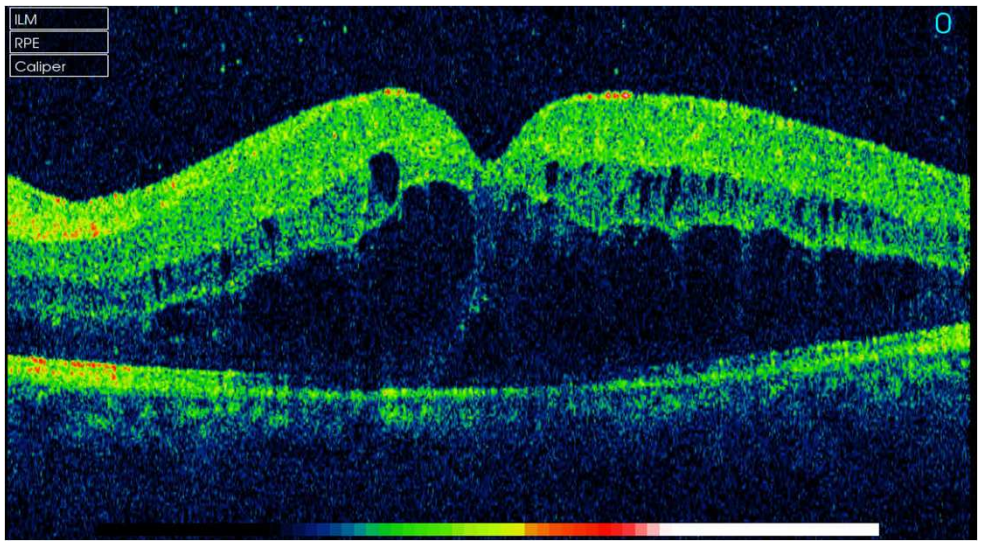
Selected case 1-Adalimumab

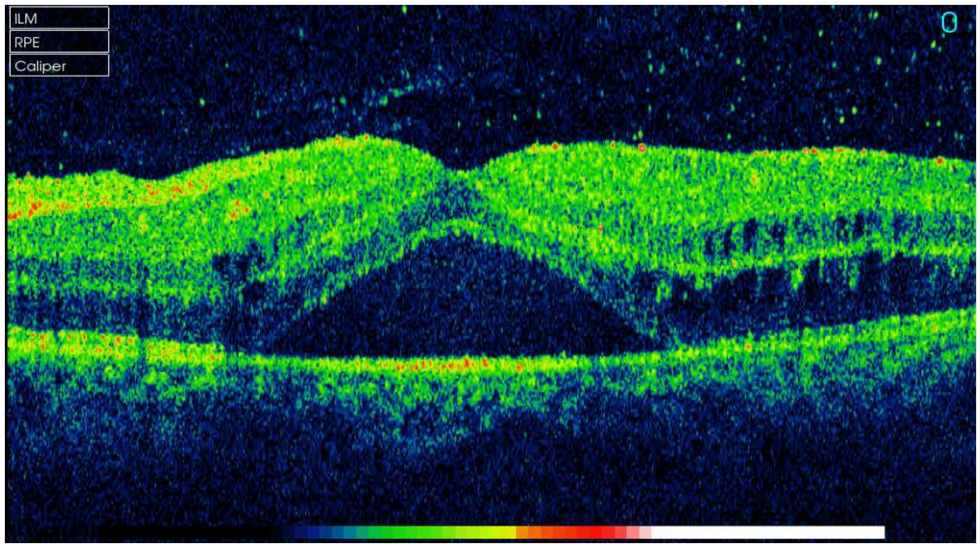


Selected case 1-Adalimumab









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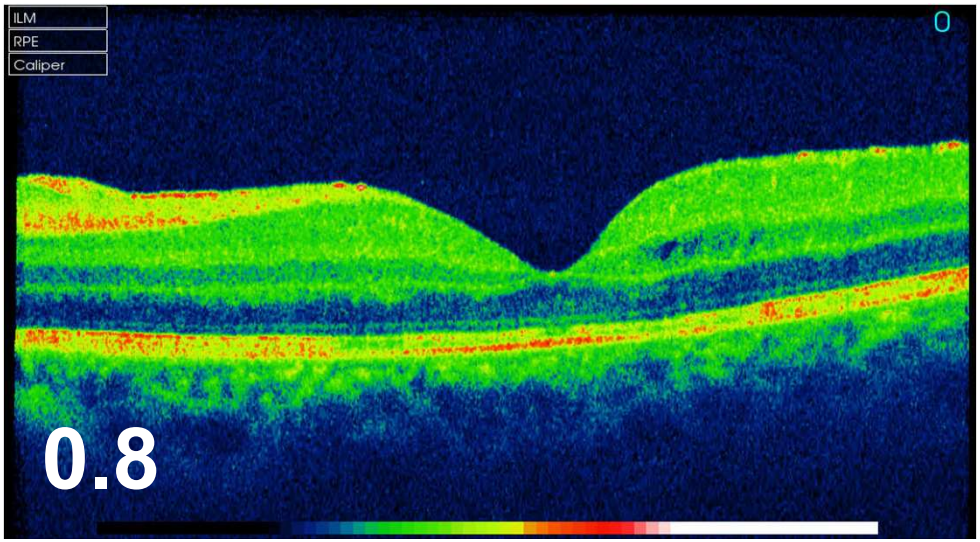
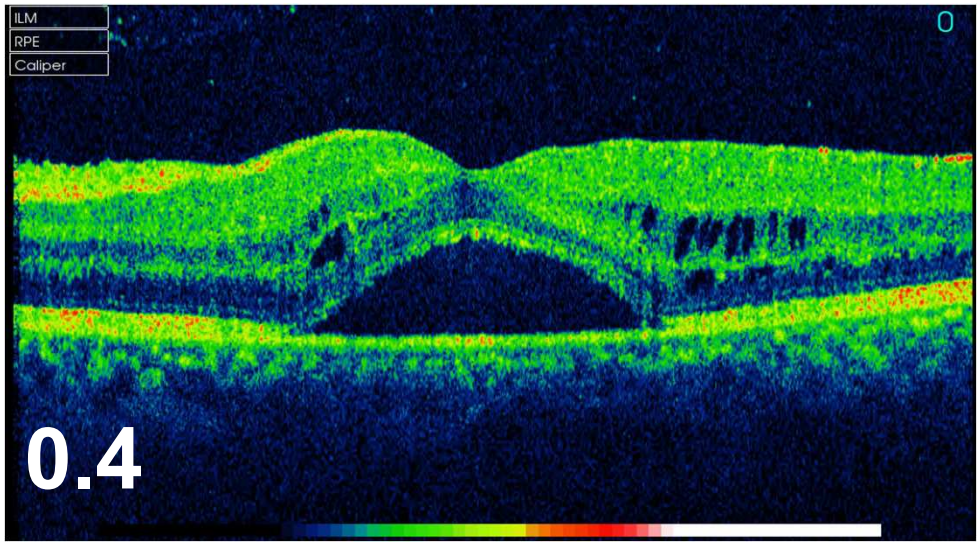
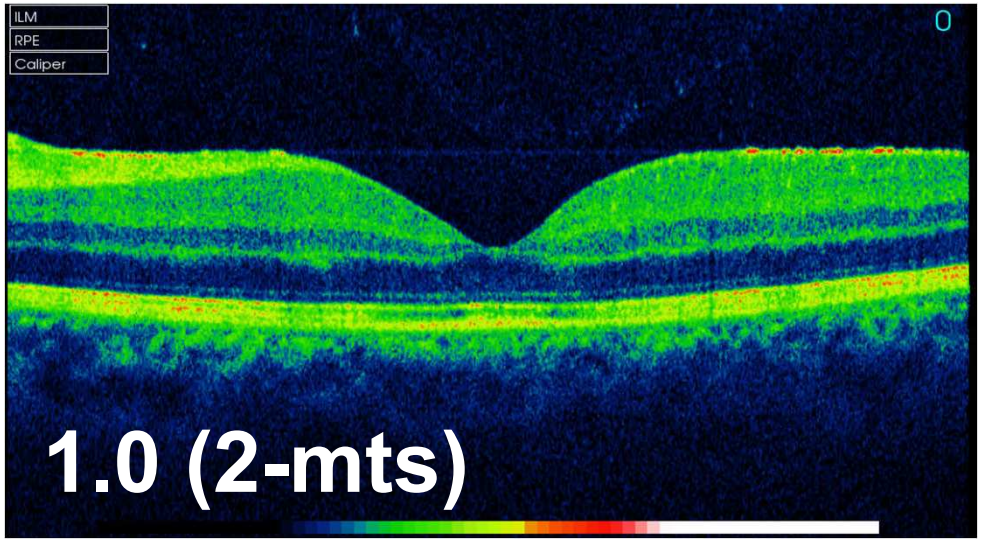
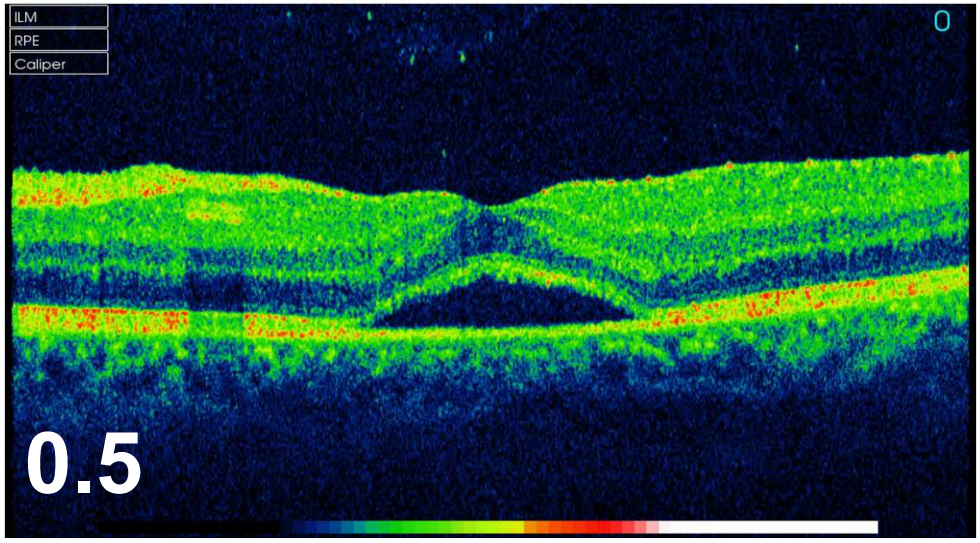
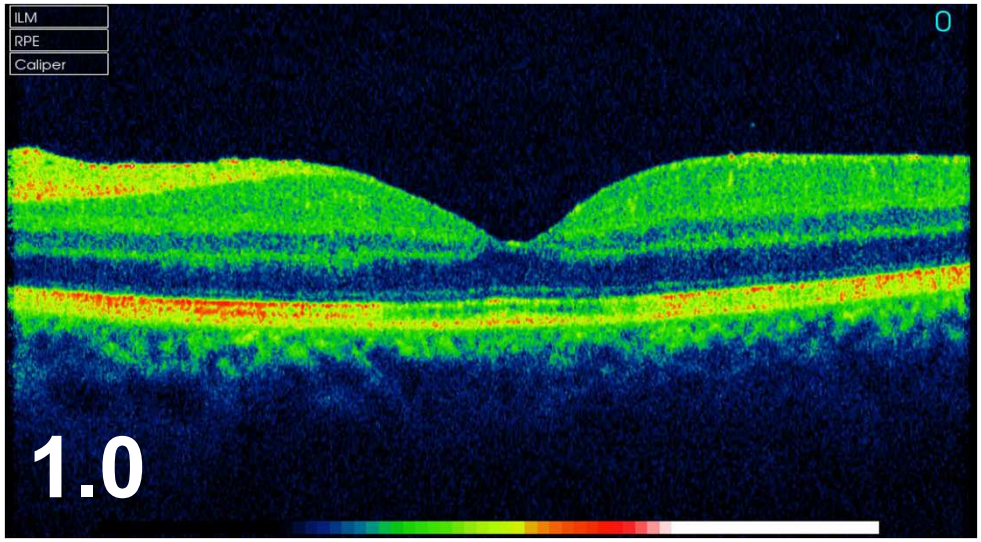


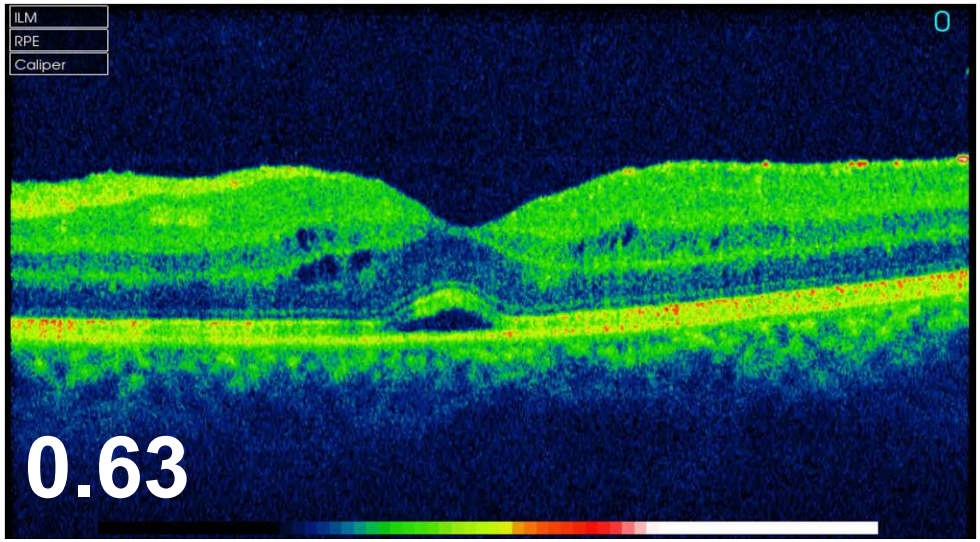


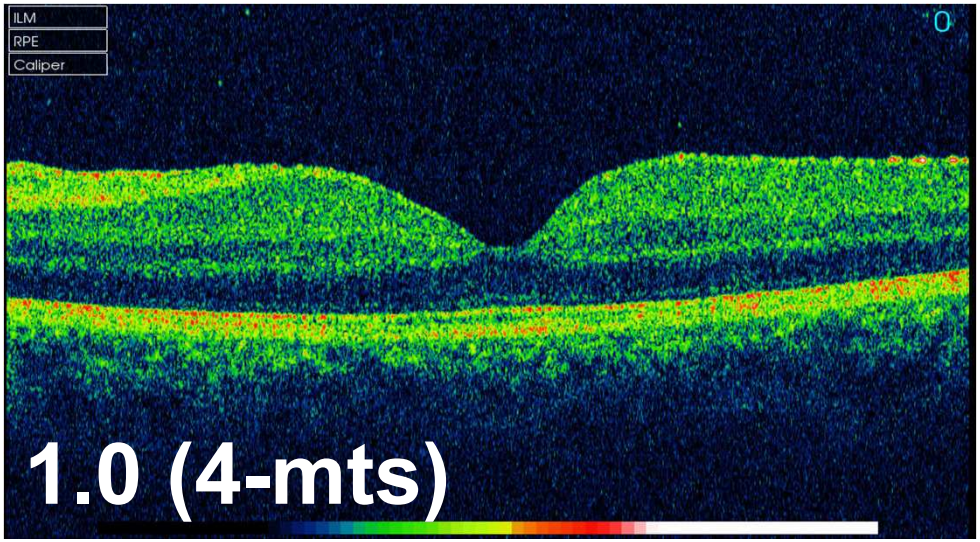


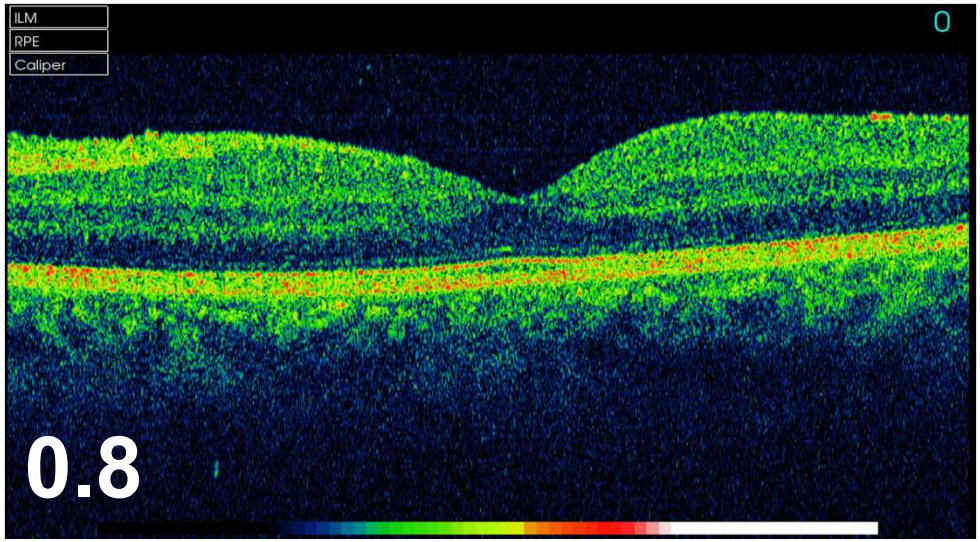


Selected case 1-Adalimumab

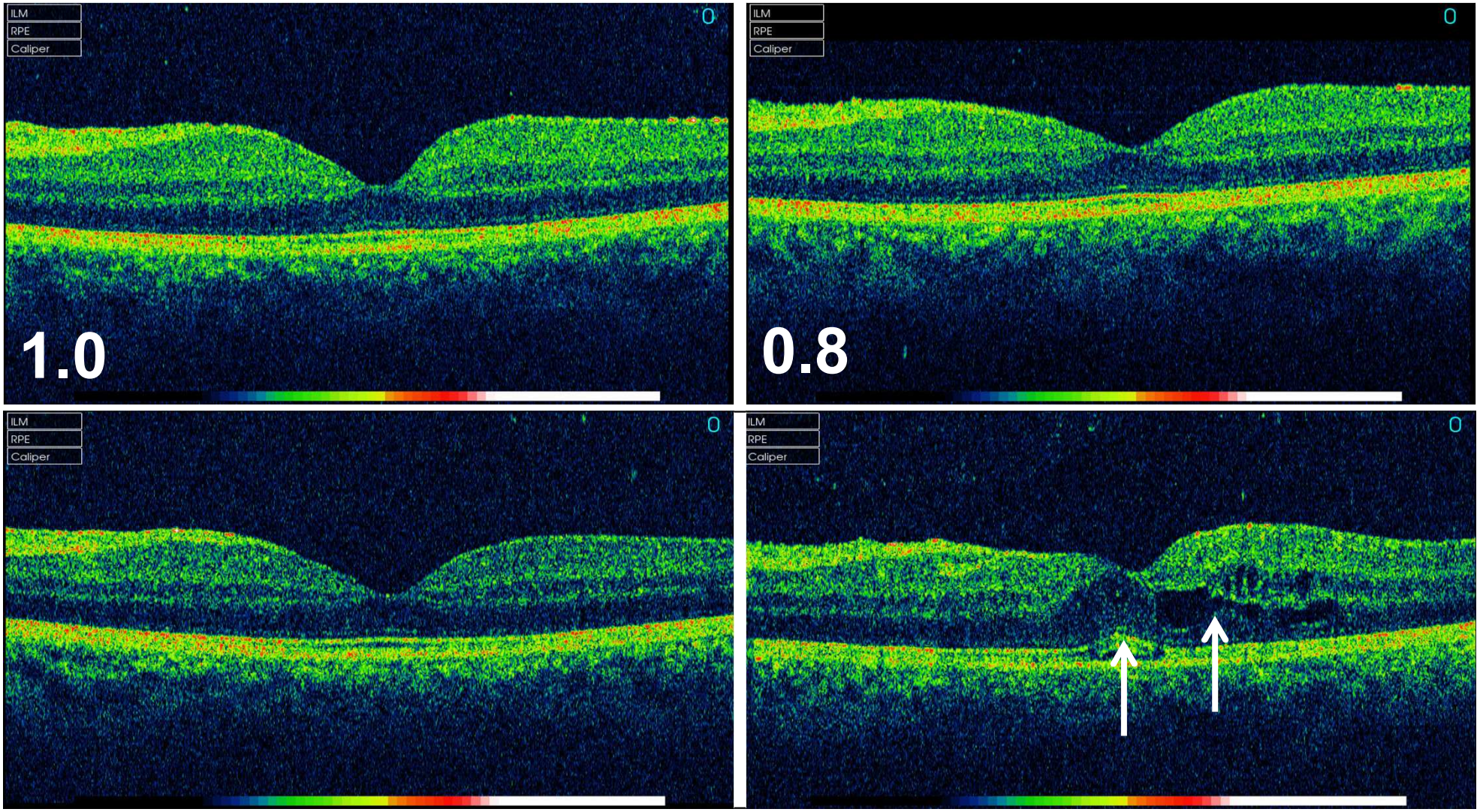








Selected case 1-Adalimumab



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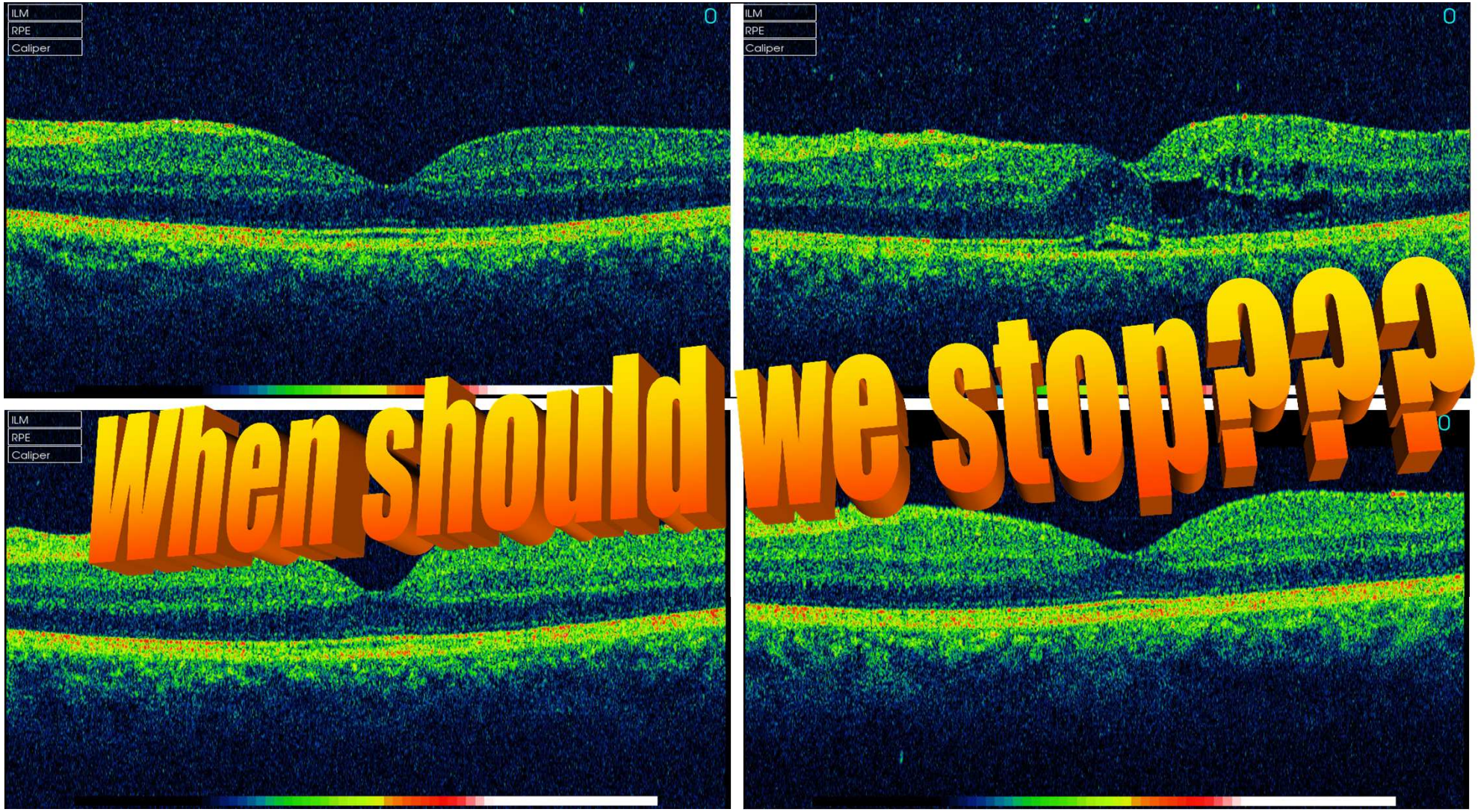

Successful treatment of an overlapping choriocapillaritis between multifocal choroiditis and acute zonal occult outer retinopathy (AZOOR) with adalimumab (Humira™)

Piergiorgio Neri, Federico Ricci, Alfonso Giovannini, Ilir Arapi, Cecilia De Felici, Andrea Cusumano & Cesare Mariotti

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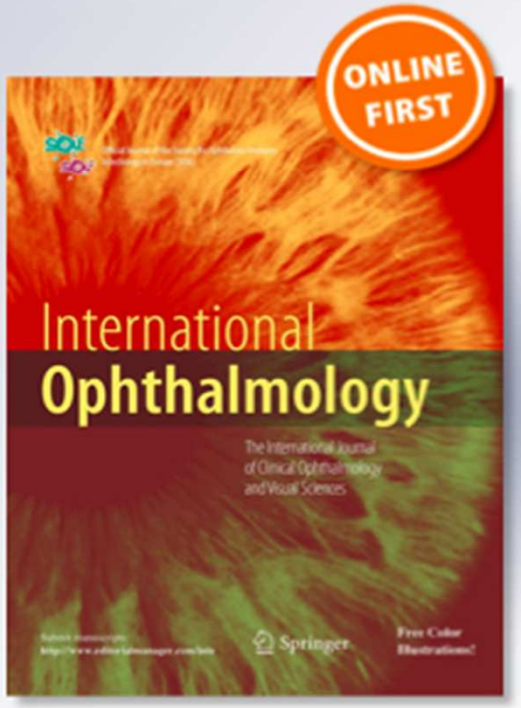

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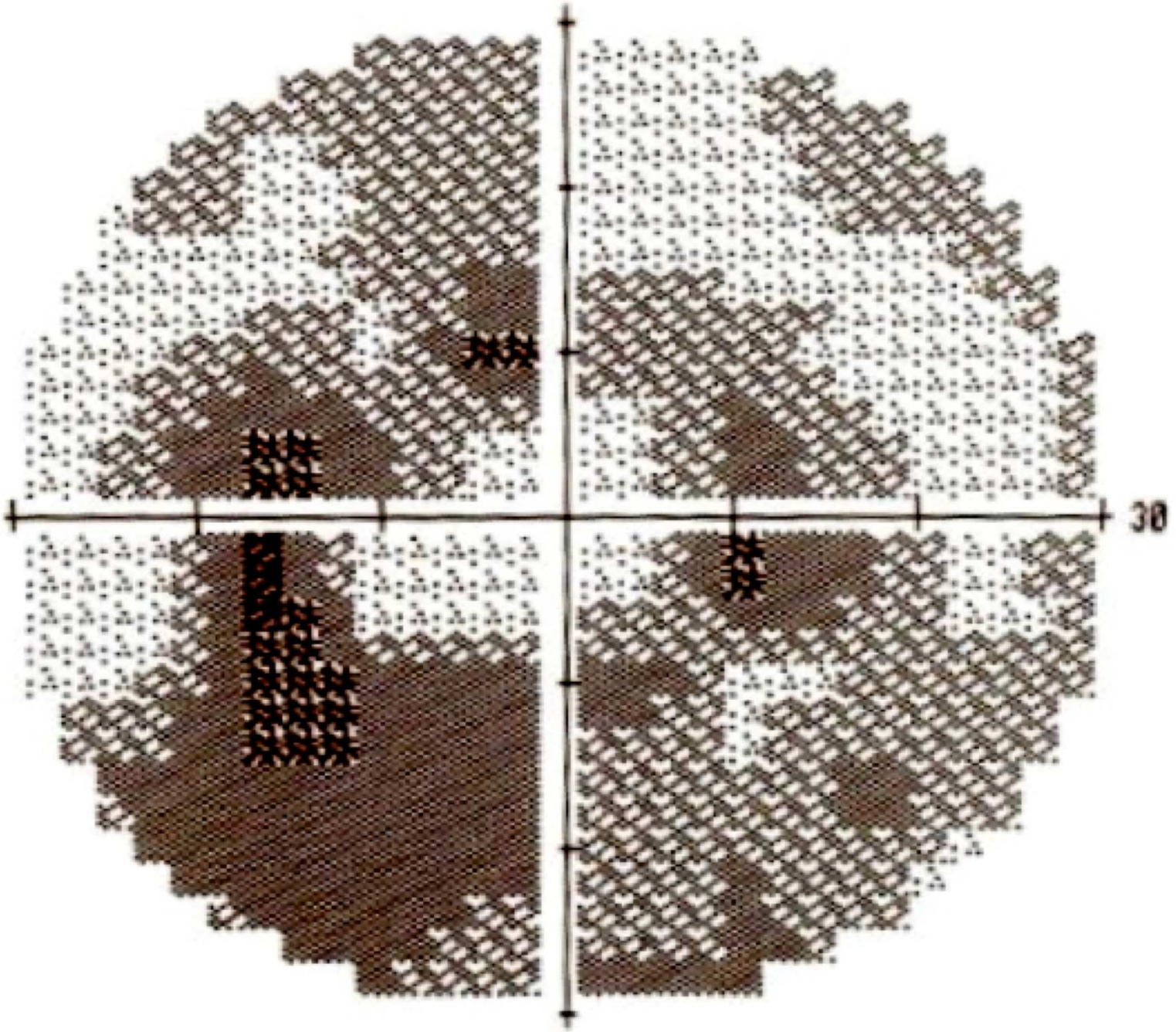
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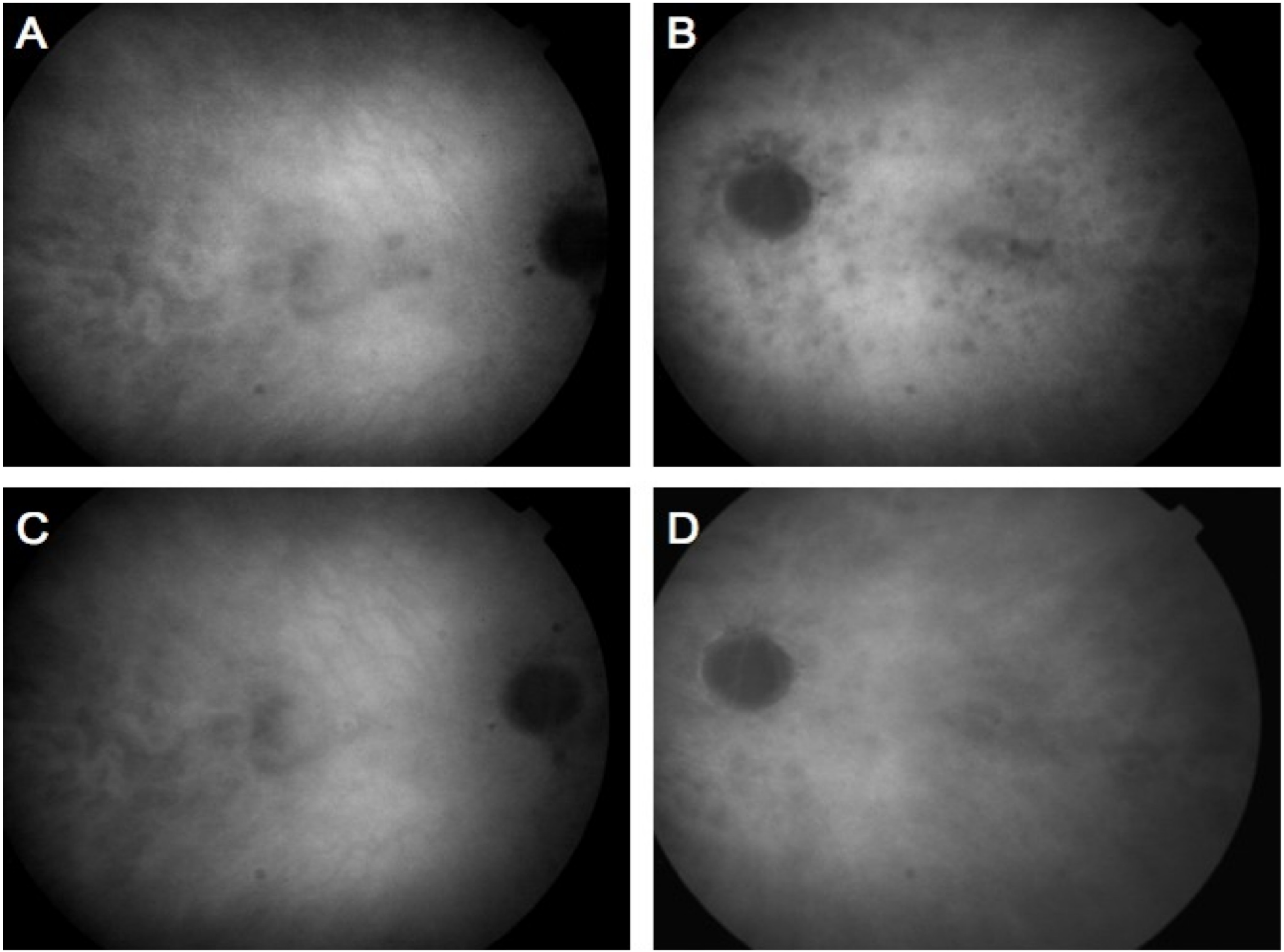
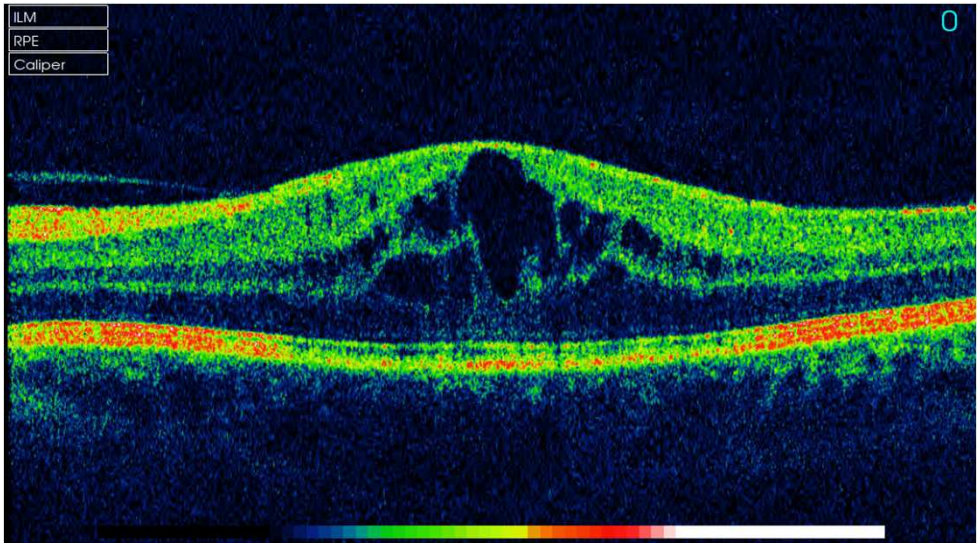
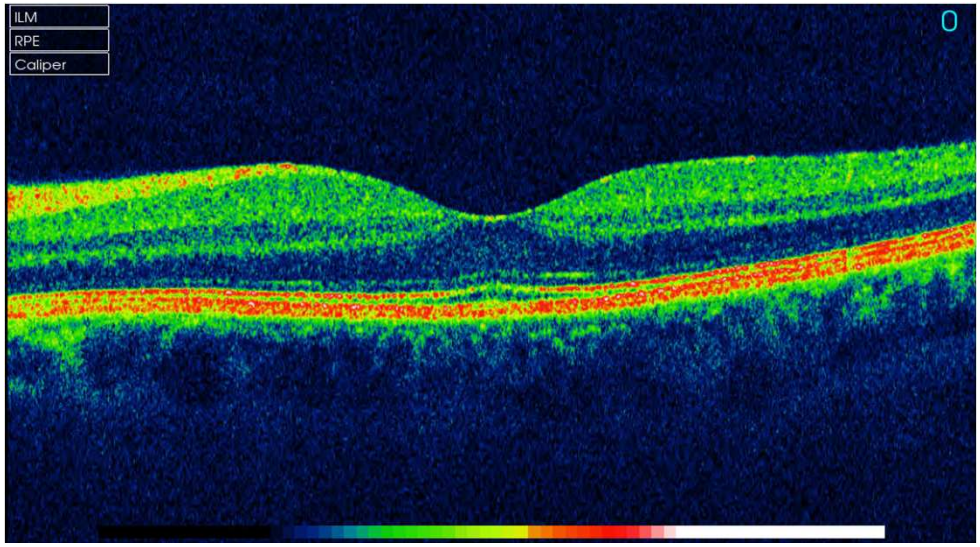

A
B
C
D

Selected case 2-HLA-27+ spondylitis associated uveitis

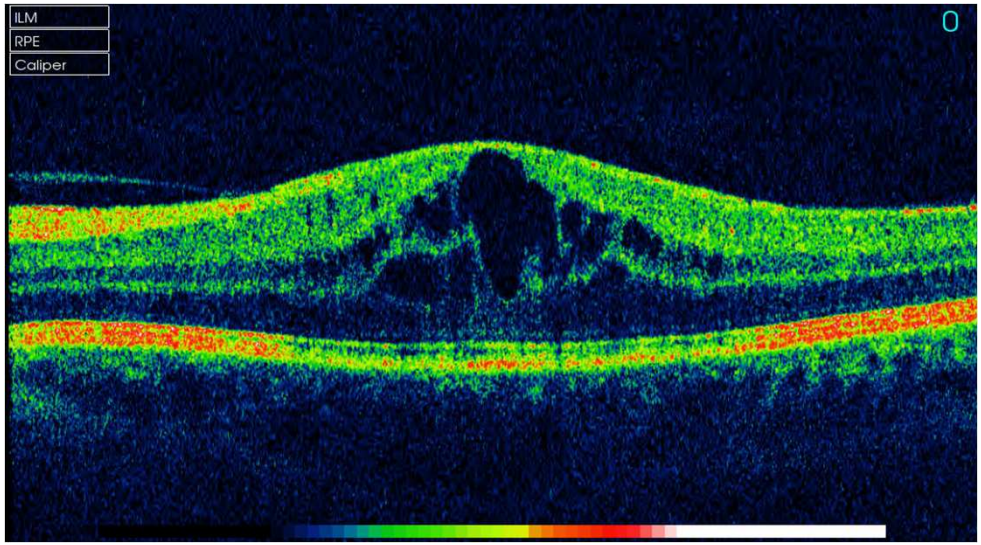


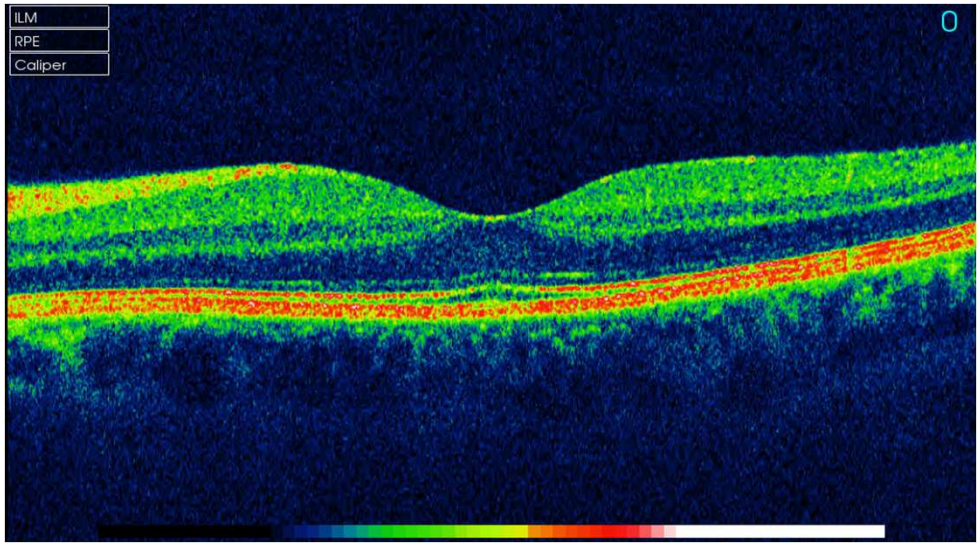


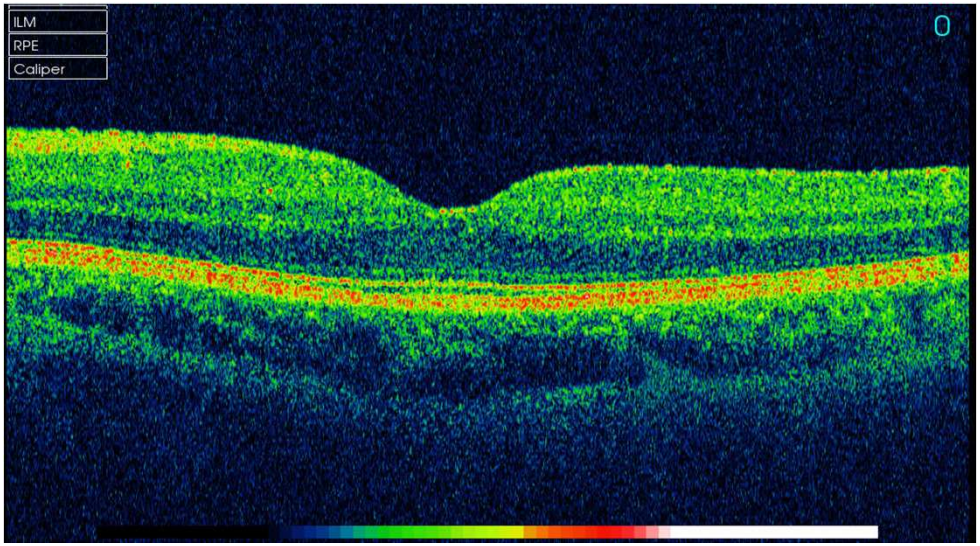
- Treatment: Infliximab (4-yr therapy)
- Joint disease under control
- Scarce control of uveitis

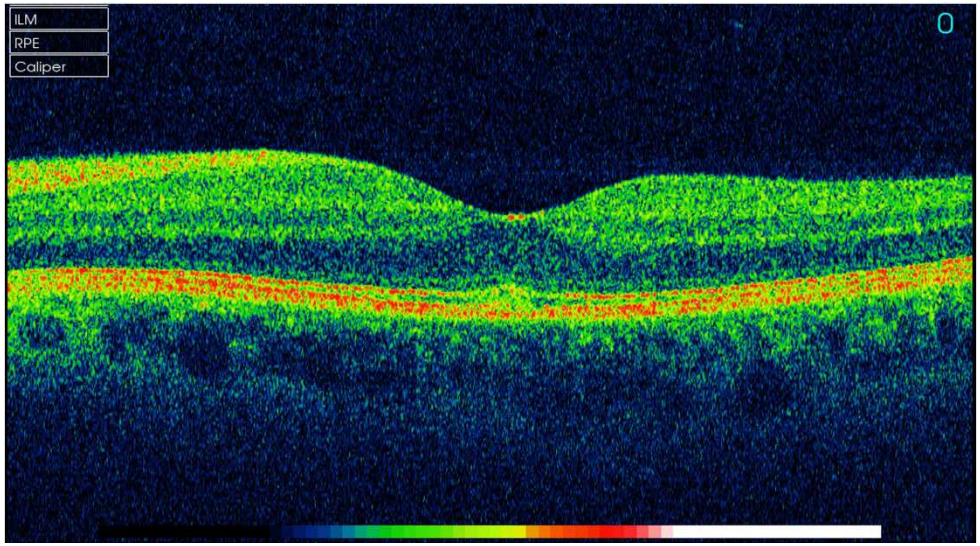
Selected case 2-HLA-27+ spondylitis associated uveitis

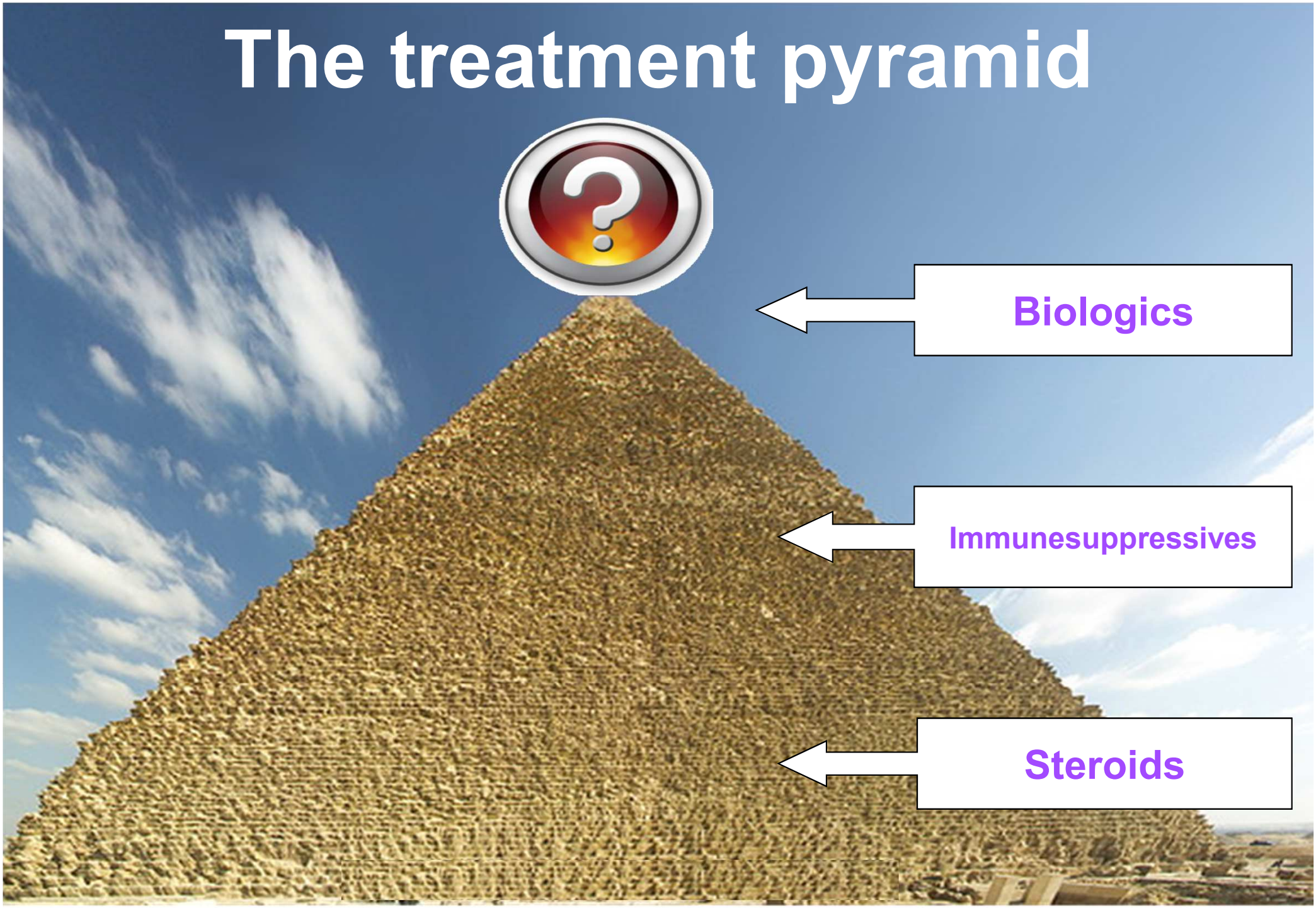
Golimumab





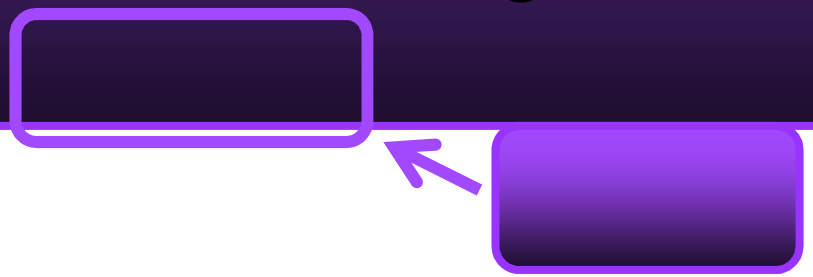


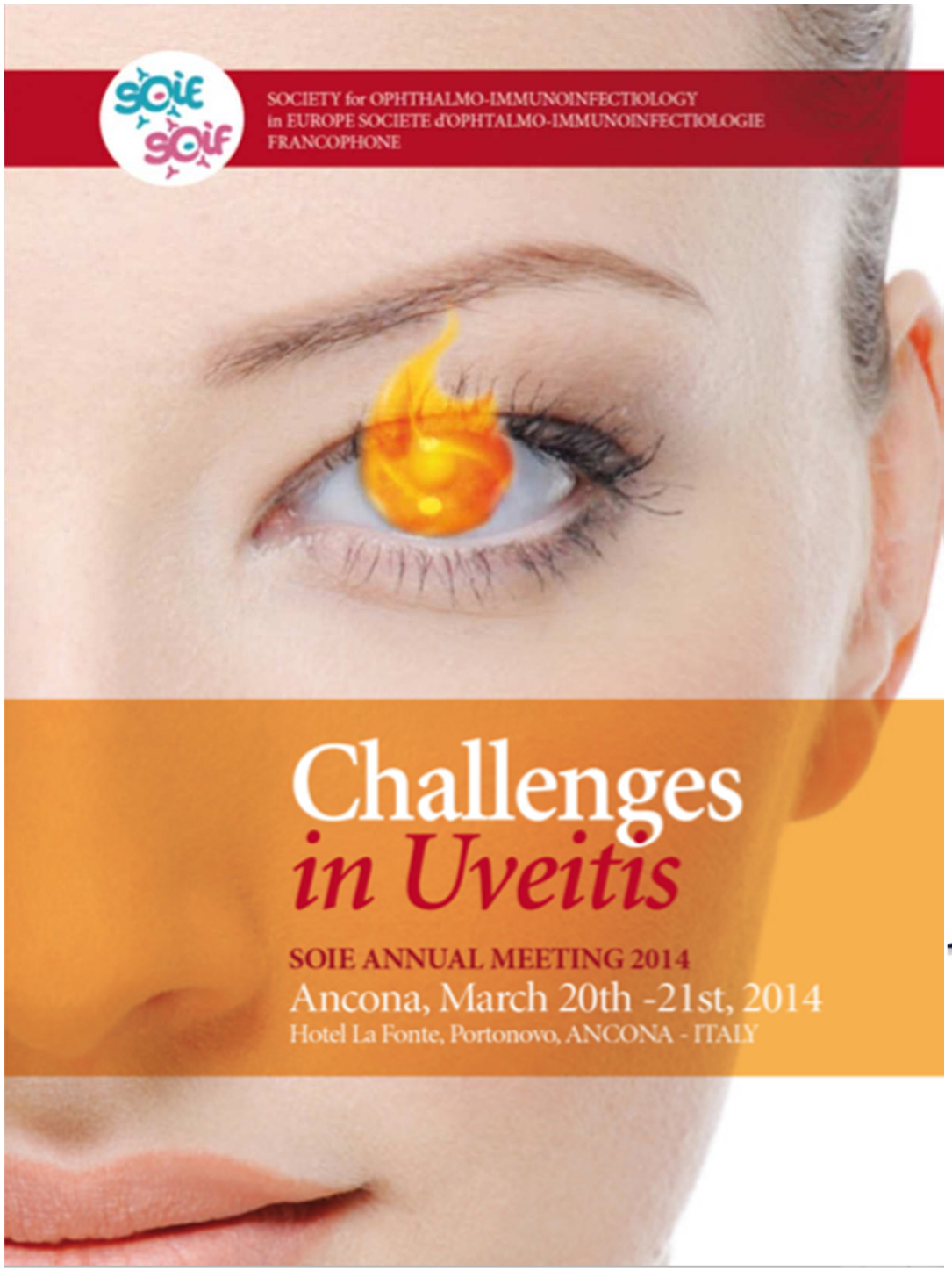



The treatment pyramid
Biologics
Immunesuppressives
Steroids

CONCLUSIONS

1. Anti-TNF-α agents are a powerful weapon for refractory cases
2. SQ Anti-TNF-α agents More userfriendly than the intravenous biologics
3. Duration issue still discussed
4. II/III line drugs for severe cases….





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