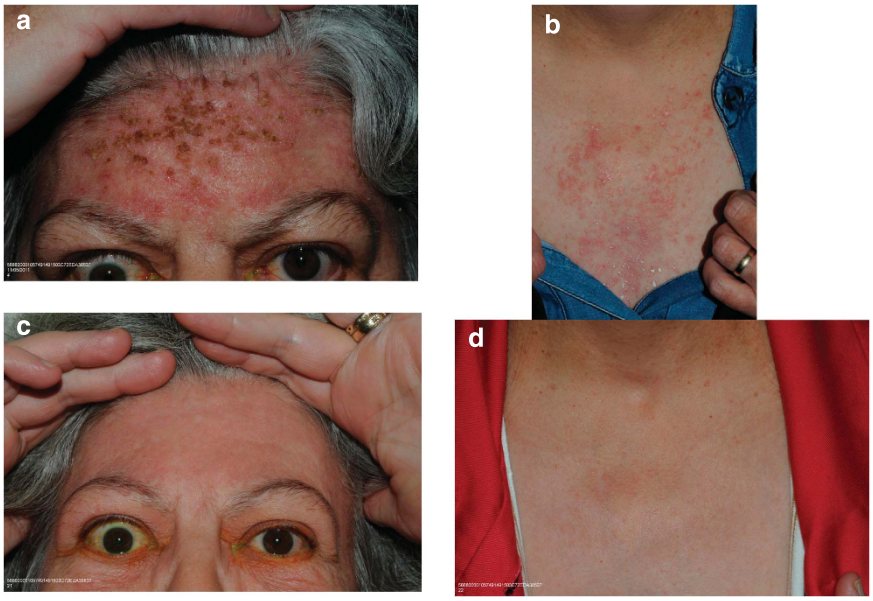

Figure 1 Composite pictures showing reactivation of Darier's disease after commencing Azathioprine treatment (a, b), with resolution following cessation of Azathioprine and treatment with acitretin (c, d).

Azathioprine is a purine analog and results in a reduced number of leukocytes owing to disruption of DNA and RNA synthesis.[4] A specific gene mutation, known to encode for a calcium pump located on the endoplasmic reticulum, has been identified in relation to Darier's disease.[2] The cause for reactivation of Darier's disease in our patient may be due to Azathioprine's pharmacological action within the endoplasmic reticulum, stimulating the Darier's disease process.

We recommend that Azathioprine is avoided in patients with known Darier's disease.

Conflict of interest

The authors declare no conflict of interest.

References

1 *Albert and Jakobiec's Principles and Practice of Ophthalmology.* 3rd ed. Saunders: Philadelphia, 2008.
2 Sakuntabhai A, Ruiz-Perez V, Carter S, Jacobsen N, Burge S, Monk S *et al*. Mutations in ATP2A2, encoding a Ca2+ pump, cause Darier disease. *Nat Genet* 1999; **21**(3): 271–277.
3 Anolik MA, Rudolph RI. Scabies simulating Darier disease in an immunosuppressed host. *Arch Dermatol* 1976; **112**(1): 73–74.
4 Gaffney K, Scott DG. Azathioprine and cyclophosphamide in the treatment of rheumatoid arthritis. *Br J Rheumatol* 1998; **37**: 824–836.

SL Levy and SM Salvi

Department of Ophthalmology, Royal Hallamshire Hospital, Sheffield, UK
E-mail: sarahfoster@doctors.org.uk

Eye (2013) **27,** 568–569; doi:10.1038/eye.2012.304; published online 1 February 2013

Sir,

Combined inhibition of tumor necrosis factor (TNF) and vascular endothelial growth factor (VEGF) for the treatment of macular edema of various etiologies: a short-term pilot study

The aim of this study is to report the 6-month anatomic and Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) response after the combination of intravitreal adalimumab and bevacizumab (IVBA) in patients with macular edema of various etiologies.

Case report

We reviewed the clinical records of consecutive patients with macular edema of various etiologies, which were treated with at least one off-label combined intravitreal injection of 1.25 mg/0.05 ml of bevacizumab and 2 mg/0.08 ml of adalimumab (Figure 1). Five consecutive patients (7 eyes), and at least 6 months of follow-up were identified and included for this analysis.

Our results are depicted in Table 1. Eyes 1 and 7 were previously treated with intravitreal bevacizumab (3 doses with 6-week intervals), with no anatomical or functional response $\geq$12 weeks from last injection. Four (57.1%) of seven eyes gained $\geq$3 ETDRS lines of BCVA. None of the patients developed systemic complications such as thromboembolic events or a cerebral vascular accident, and none developed any ocular complication.

Comment

Sfikakis *et al*[1] reported an improvement in visual acuity and macular edema in four patients with refractory DME, following two intravenous infusions of infliximab (5 mg/kg) given 1 month apart. Wu *et al*[2] did not find any visual benefit with either 1 or 2 mg of infliximab or 2 mg of adalimumab in eyes with refractory DME. In addition, a high rate of intraocular inflammation was seen in eyes injected with infliximab.

Androudi *et al*[3] reported five patients with refractory cystoid macular edema secondary to noninfectious uveitis that were treated with intravitreal adalimumab for 3 months with no apparent benefit. There were no

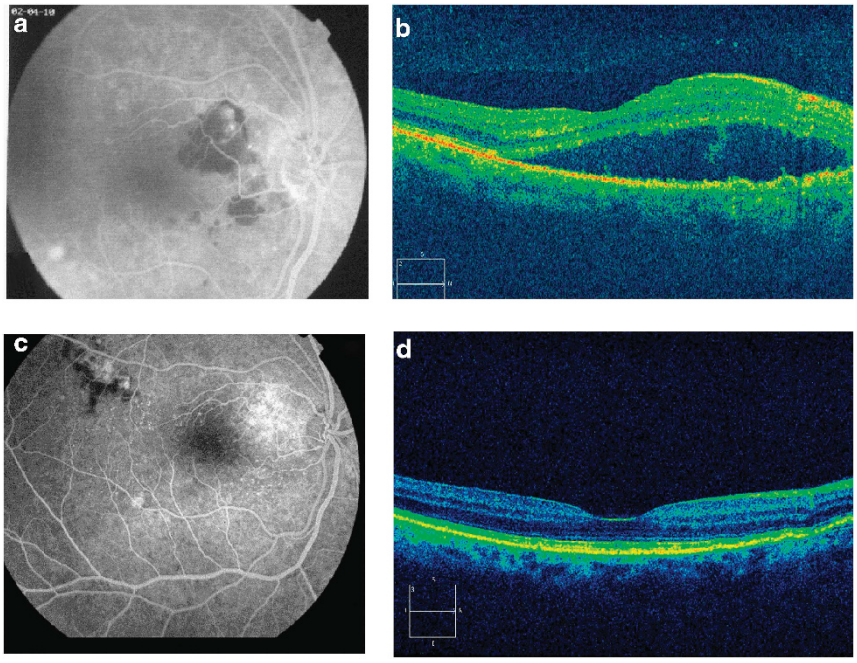

Figure 1 (a) Late phase fluorescein angiogram demonstrates an extrafoveal choroidal neovascular membrane associated with age-related macular generation with subretinal fluid, with a best-corrected visual acuity (BCVA) of 20/80. (b) Spectral domain optical coherence tomography (SD-OCT) of the lesion shows a hyporreflective image confirming subretinal fluid at baseline. (c) Late phase fluorescein angiogram, and (d) SD-OCT demonstrate a complete resolution of subretinal fluid, with a BCVA of 20/25 at 6 months of follow up, after doses of intravitreal adalimumab and bevacizumab. There is a new area of hypo- and hyperfluorecence supero-temporal to the fovea without leakage (c).

Table 1 Patient's demographics, etiology, and clinical findings before and after IVBA

Patients/ Eye #	*Lat*	*Age (years)*	*Gender*	*Duration of ME (months)*	*Etiology*	*ETDRS BCVA*				*OCT CMT*				*# of Injections*
						Baseline	*1 month*	*3 months*	*6 months*	*Baseline (μ)*	*1 month (μ)*	*3 months (μ)*	*6 months (μ)*	
1/1	OD	71	F	08	PMCE	20/125	20/63	20/63	20/63	239	245	280	283	1
1/2	OS	71	F	10	PMCE	20/63	20/63	20/80	20/80	233	250	272	273	1
2/3	OD	51	M	06	DME	20/80	20/40	20/40	20/40	505	308	320	321	2
2/4	OS	51	M	06	DME	CF	20/100	20/80	20/80	664	310	335	332	2
3/5	OS	69	M	02	CRVO	20/200	CF	CF	CF	502	510	516	520	4
4/6	OD	67	F	01	AMD	20/80	20/25	20/25	20/25	385	208	224	220	4
5/7	OD	82	M	07	AMD/ BRVO	20/200	20/200	20/200	20/200	289	300	310	310	2

Abbreviations: AMD, exudative age-related macular degeneration; BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; CMT, central macular thickness; CRVO, central retinal vein occlusion; DME, diabetic macular edema: ETDRS, Early Treatment Diabetic Retinopathy Study; F, female; IVBA, intravitreal bevacizumab and adalimumab; lat, laterality; M, male; ME, macular edema; OCT, optical coherence tomography; OD, right eye; #, number; OS, left eye; PMC, pseudophakic cystoid macular edema.

important adverse events reported in this small group of patients.

No important adverse events, including inflammation, were reported in our current series.

The limitations of our study include its small sample size, and retrospective nature. In addition, although our study suggests there is a benefit from combined VEGF and TNF-α inhibition, it is unclear if the same benefit could have been obtained with either agent or only with both. Furthermore, several of the etiologies have a documented natural history to suggest that spontaneous resolution is possible. However, two eyes did not respond to prior treatment with bevacizumab alone and did respond to combined VEGF and TNF-α inhibition. Our results warrant further study.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

This study was supported in part by the Arevalo-Coutinho Foundation for Research in Ophthalmology, Caracas, Venezuela.

References

1 Sfikakis PP, Markomichelakis N, Theodossiadis GP, Grigoropoulos V, Katsilambros N, Theodossiadis PG. Regression of sight-threatening macular edema in type 2 diabetes following treatment with the anti-tumor necrosis factor monoclonal antibody infliximab. *Diabetes Care* 2005; **28**: 445–447.

2 Wu L, Hernandez-Bogantes E, Roca JA, Arevalo JF, Barraza K, Lasave AF. Intravitreal tumor necrosis factor inhibitors in the treatment of refractory diabetic macular edema: a pilot study from the Pan-American Collaborative Retina Study Group. *Retina* 2011; **31**: 298–303.

3 Androudi S, Tsironi E, Kalogeropoulos C, Theodoridou A, Brazitikos P. Intravitreal adalimumab for refractory uveitis-related macular edema. *Ophthalmology* 2010; **117**: 1612–1616.

JF Arevalo[1,2], MA Serrano[3] and L Wu[4]

[1]Retina Division, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[2]The Vitreoretinal Division, King Khaled Eye Specialist Hospital, Riyadh, Kingdom of Saudi Arabia
[3]The Retina and Vitreous Service, Clinica Oftalmologica Centro Caracas, Caracas, Venezuela
[4]The Instituto de Cirugia Ocular, San Jose, Costa Rica
E-mail: arevalojf@jhmi.edu

Presented in part at the 44th Retina Society Annual Scientific Meeting, Rome, Italy, September 2011.

Eye (2013) **27,** 569–571; doi:10.1038/eye.2012.301; published online 18 January 2013

Sir,

Adherence to NICE guidelines for new glaucoma referrals

The NICE guidelines for glaucoma[1] gave key priorities for implementation in the management of glaucoma and ocular hypertension. It includes the minimum assessments and investigations. We assessed the adherence to NICE glaucoma guidelines in a university hospital. In addition, we assessed variation of investigations in relation to grade of doctor and final documentation of diagnosis.

The records of 50 consecutive new referrals for glaucoma, from September to December 2009, were reviewed. The records of the 25 patients who were diagnosed with glaucoma (including suspects) or ocular hypertension were further analysed. A pro forma of the NICE guidelines was created, which included age and sex of patient, investigations, documentation of diagnosis, and grade of doctor.

Thirty six percent of patients were seen by a glaucoma specialist. Overall, 48% were diagnosed with glaucoma, 16% were suspects, 16% had ocular hypertension, 4% had pigment dispersion syndrome, and 16% had no clear diagnosis. All patients had intraocular pressure measurement by Goldmann applanation tonometry, 64% had central corneal thickness measurements, and 76% had gonioscopy. One-third of patients diagnosed with glaucoma did not have a CCT measurement documented. Visual fields were performed in 96%, but only 32% were dilated for disc assessment and fundoscopy. The 68% of patients who were not dilated for fundoscopy were seen either by non-glaucoma consultants or trainees. Only 25% of those diagnosed with glaucoma had optic disc imaging with scanning laser polarimetry (GDx VCC).

Adherence to the NICE glaucoma guidelines is varied and depends on whether the patient is seen by a non-glaucoma or a glaucoma specialist. The key priorities highlighted by the guidelines need to be reinforced to improve adherence for a more adequate patient assessment. This sequentially can lead to fewer patients receiving avoidable follow-up appointments.

Goldmann IOP and VFs were well performed and documented. Gonioscopy, optic nerve imaging, pupillary dilation for optic nerve and fundus assessment, and CCT were poorly documented, which therefore requires attention. Although this consists of a small amount of data, it clearly reflects areas of weakness that may be demonstrated in other centres. This letter highlights possible areas for further training.

Conflict of interest

The authors declare no conflict of interest.

Reference

1 UK National Institute of Health and Clinical Excellence. Glaucoma: diagnosis and management of chronic open angle glaucoma and ocular hypertension 2009. (available at http://www.nice.org.uk/CG85).