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Letters to the Editor

Intravitreal aflibercept for treatment of macular oedema associated with immune recovery uveitis

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Immune recovery uveitis (IRU) is a part of immune reconstitution inflammatory syndrome, which is characterized by worsening or unmasking of opportunistic infections after quick improvement of immune functions in previously immunosuppressed patients. Immune recovery uveitis (IRU) is most common in patients with human immunodeficiency virus (HIV) (Kempen et al. 2006), but has also been reported in HIV-negative patients. The most common pathogen associated with IRU is cytomegalovirus (CMV). Clinical features of IRU include anterior uveitis and vitritis complicated by development of cataract, epiretinal membranes and cystoid macular oedema (CME). Patients with IRU had a 20-fold higher risk of CME, which represents a major cause of visual loss in HIV-infected patients (Kempen et al. 2006). Treatment of IRU-associated CME is challenging. Mostly, corticosteroids in various administration routes are used, but this approach obviously includes a risk of reactivation of infection.

We observed a beneficial effect of aflibercept in patients in five consecutive patients (seven affected eyes) with IRU-induced CME.

Clinical data of included patients are given in Table 1. Four patients were HIV-positive, and all had previously treated CMV retinitis. All had a low nadir of their CD4 lymphocyte counts (<20/mm^3) before start of their antiretroviral therapy. One additional HIV-negative patient developed bilateral CMV retinitis during the aplastic phase after chemotherapy and stem cell transplant for acute myeloid leukaemia. Intravitreal bevacizumab was administered in four patients (five eyes): without improvement of CME in three and with transient improvement in one patient. Aflibercept was given as a single injection, and decision to repeat the injection was based on OCT findings. Patients were initially followed every 4 weeks and gradually the intervals between the examinations were increased.

All treated eyes achieved a resolution of CME and demonstrated improved visual acuity. Resolution of CME was noted after a single aflibercept injection even in eyes with ineffective previous treatment modalities (six eyes treated with various combinations of periocular and systemic corticosteroids, acetazolamide, somatostatin analogue octreotide and intravitreal bevacizumab). In two patients receiving aflibercept shortly after onset of CME, a long-term remission was achieved, which did not require any additional therapy.

Table 1. Characteristics of patients with immune recovery uveitis after treated cytomegalovirus retinitis.

Gender and age at onset IRU (HIV status)	Cause of immune suppression	Previous treatment CME*	Affected eye(s)	Duration CME before aflibercept administration	VA before aflibercept administration	Final VA in decimals	Central macular thickness before aflibercept therapy (µm)	Final central macular thickness (µm)	N of aflibercept injections	Follow-up since start of aflibercept (weeks)
F, 48 years, HIV–[§]	Acute myeloid leukaemia, stem cell transplantation	Acetazolamide, oral and periocular corticosteroids, octreotide, intravitreal bevacizumab	RE	3 months	0.5	1.0	453	244	18	224
			LE	<4 weeks	0.5	1.0	736	276	3	228
M, 62 years, HIV+	AIDS	Acetazolamide, oral corticosteroids, intravitreal bevacizumab	RE	8 months	0.9	1.0	471	254	3	110
			LE	5 months	0.05	0.6	527	228	1	104
M, 50 years, HIV+	AIDS	Acetazolamide, oral prednisone, intravitreal bevacizumab	RE	< 4 weeks	0.7	1.2	578	313	6	124
M, 47 years, HIV+	AIDS	Acetazolamide, oral nonsteroidal anti-inflammatory drugs, intravitreal bevacizumab	LE	5 years	0.4	0.6	383	328	3	80
M, 45 years, HIV+[†]	AIDS	None[‡]	LE	4 months	0.7	0.9	371	239	2	24

AIDS = acquired immune deficiency syndrome; CME = cystoid macular oedema; HIV = human immunodeficiency virus; IRU = immune recovery uveitis; OCT = ocular coherence tomography; VA = visual acuity.
* All affected eyes were treated by topical corticosteroid and nonsteroidal anti-inflammatory drops in various dosages.
† Other eye destroyed by extensive CMV retinitis.
‡ In this patient, we chose aflibercept as a consequence of earlier failure of other treatment options and success of aflibercept in other IRU patients.
§ HIV-negative patient developed bilateral CMV retinitis during the aplastic phase after chemotherapy and stem cell transplant for acute myeloid leukaemia. This patient developed IRU four months after the activity of her CMV retinitis subsided and had at that time negative aqueous PCR results for CMV.

The increased levels of intraocular proangiogenic factors, such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), were repeatedly reported in ocular inflammation (Kozak et al 2017). These factors, next to their proangiogenic activity, also activate endothelial cells and promote cell proliferation, migration and vascular permeability. The anti-inflammatory effect of intraocular bevacizumab and aflibercept was previously documented (Papadopoulos et al. 2012; Sato et al. 2018). Aflibercept has a markedly higher affinity for VEGF-A than bevacizumab and ranibizumab, and moreover, aflibercept binds VEGF-B and PlGF (Papadopoulos et al. 2012). It is possible that these differences are responsible for a better effect of aflibercept in patients with IRU-induced CME.

Several cases of HIV-infected patients were described with previously unrecognized CMV retinitis who developed symptoms of active CMV retinitis together with active inflammatory signs attributed to IRU shortly after the start of antiretroviral treatment (Rangel et al. 2015). Treatment modality with aflibercept might be especially of value in patients with uncertain activity of CMV retinitis.

Our study has multiple shortcomings. First, the number of patients is very small, and patients were not treated in systematic fashion. Despite our limitations, we believe that consideration should be given to the use of intravitreal aflibercept in patients with IRU, especially in those who have failed other treatments.

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B12 deficiency, optic neuropathy and cyanocobalamin nasal spray

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Editor,

Vitamin B12 in the form of cyanocobalamin (CNCbl) nasal spray was approved in 2005 (Nascobal® FDA). This is the first report describing the evolution of optic neuropathy in a patient whose low serum vitamin B12 was supplemented by CNCbl nasal spray.

A 60-year-old man with chronic tobacco and alcohol use noted progressive visual blur in his left eye. Blood testing revealed mild macrocytosis (107 fl; reference 81–99 fl) and low vitamin B12 (116 pmol/l; reference 138–652 pmol/l). Due to longstanding gastric problems, vitamin B12 supplementation was started by nasal spray (CNCbl 500 μg/0.1 ml in one nostril once per week). The cause of visual blur was not determined at this time.

Subsequent ophthalmologic examination showed visual acuity of 20/20 in the right eye (RE) and 20/32 in the left eye (LE). Biomicroscopy and funduscopy were normal. Macular and optic nerve optical coherence tomography was normal. Visual field testing showed small bilateral central scotomas (Fig. 1A) and an optic neuropathy was suspected. Neuroimaging, serologic testing and molecular analysis excluded other causes of optic neuropathy. The patient confirmed taking vitamin B12 supplementation.

Two months later, the patient was referred for neuro-ophthalomologic consultation. Visual acuity was 20/40 RE and counting fingers LE with enlarging central scotomas (Fig. 1B). Bilateral dyschromatopsia and early optic atrophy were noted. Serum level of vitamin B12 was still low (holotranscobalamin 36 pmol/l; reference> 50 pmol/l). Treatment was changed to intramuscular hydroxycobalamin (OHCbl). One week later, visual acuity was improved to 20/32 RE and 20/100 LE. Three months later, serum B12 level was normalized (holotranscobalamin level > 128 pmol/l). Six months later, central scotomas were nearly resolved (Fig. 1C) and acuity was 20/25 RE and 20/40 LE.

The CNCbl (B12) nasal spray is recommended for maintenance therapy after intramuscular B12 treatment in adult patients with pernicious anaemia without neurologic involvement or as primary treatment of adult patients with vitamin B12 deficiency not due to pernicious anaemia (Nascobal® FDA). In a small case series, CNCbl nasal spray effectively increased serum B12 levels and improved symptomatic paresthesias (Zamuner et al. 2014).

In contrast to synthetically derived CNCbl, OHCbl is a natural form with better tissue bioavailability (Paul & Brady 2017). In patients with asymptomatic B12 deficiency who were given three consecutive weekly doses of 1500 μg OHCbl nasal spray, a sustained increase in serum level was noted after one dose and became normalized following the second dose (Slot et al. 1997). OHCbl is not, however, commercially available as nasal spray.