Diabetic macular oedema (DMO) is an important cause of vision loss and challenges remain in the treatment of this progressive disease. Corticosteroids provide a comprehensive treatment approach, lowering the concentration of inflammatory cytokines and growth factors such as vascular endothelial growth factor (VEGF). However, intravitreal injections are often short-lived and are associated with intraocular side effects. The ILUVIEN® intravitreal implant contains fluocinolone acetonide and is administered by injection into the vitreous cavity. Its efficacy and safety have been demonstrated in clinical studies, and a subgroup analysis has shown that it is particularly beneficial in patients with long-standing DMO – a group with poor visual outcomes and limited treatment options. As a result, the ILUVIEN implant has been approved in Europe for the treatment of visual impairment due to chronic DMO considered insufficiently responsive to available therapies. These data have been supported by real-use clinical experience and two cases are presented that demonstrate the effectiveness of the ILUVIEN implant in two patients where prior therapies including ranibizumab have not produced a sustained beneficial effect.

Abstract
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Keywords
Corticosteroids, ILUVIEN®; fluocinolone acetonide, diabetic macular oedema

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Diabetic macular oedema (DMO) is the primary cause of vision loss in diabetic retinopathy (DR), which is the leading cause of blindness in the working population among patients aged 20 to 70 years in developed countries. The global prevalence of DR among individuals with diabetes is around 35%, with DMO present in 6.8%. The prevalence rates of DR were significantly higher in individuals with type 1 diabetes compared with type 2 (77.3% versus 25.2%). The total number of people with diabetes worldwide is projected to rise from 366 million in 2012 to 522 million in 2030, a factor of 1.5 within 20 years. It is anticipated that the annual incidence of diagnosed DMO will increase in line with the increase in diabetes, suggesting that 37.5 million people worldwide will have DMO by 2030, and will represent a substantial global health and economic burden. This article aims to examine the treatment options for DMO and to assess the clinical data in support of the ILUVIEN® intravitreal implant, as well as discussing two clinical cases illustrating the use of the ILUVIEN implant.

Pathophysiology of Diabetic Macular Oedema
DMO is a consequence of persistent hyperglycaemia and, if untreated, results in a rapid decline in visual acuity (VA). The pathophysiology of the condition is a complex process whereby hyperglycaemia initiates molecular pathways leading to dilated capillaries, retinal microaneurysms, and loss of pericytes. This results in impairment of the blood-retinal barrier (BRB) and increased vascular permeability, causing fluid to accumulate in retinal tissue. At early disease stages, vascular endothelial growth factor (VEGF) is the major driver of retinal changes. However, a large number of physiological and molecular factors, including angiogenesis, inflammation and oxidative stress, are involved in the pathogenesis of DMO. In chronic DMO, heightened inflammation is primarily responsible for the perpetuation of retinal changes.

Diabetic Macular Oedema Treatment Options
In addition to tight glycaemic control to reduce glycated haemoglobin (HbA1c) levels, prevention of visual loss depends on the timely detection of DMO and immediate initiation of adequate therapy. The severity of DMO is assessed by measuring foveal thickness and the decline in VA. Current treatment options for DMO include laser photocoagulation and the use of intravitreal drugs. Grid macular photocoagulation was the standard of care for over 25 years, but VA gains were only modest. Data from clinical studies showed that around 40% of eyes gained between 0 and 5 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale over a 2-year period.

In terms of pharmacological treatment of DMO, ranibizumab (an anti-angiogenic agent) was approved by the European Medicines Agency (EMA) in 2011 for the treatment of vision impairment secondary to DMO, after demonstrating improvements in VA and reductions in retinal thickness in clinical trials. The Ranibizumab Injection in Subjects with Type 2 Diabetes (RIDE) and Ranibizumab Injection in Subjects with Type 1 Diabetes (RISE) trials were the first randomized, placebo-controlled clinical trials to demonstrate the sustained benefits of ranibizumab in treating DMO with a documented 30% reduction in the risk of visual loss (≥15 letters) at 24 months.

In the RIDE study, ranibizumab was administered monthly for 24 months. The primary endpoint was the proportion of eyes that showed a ≥15-letter improvement in VA from baseline at the 12-month visit. The results showed that ranibizumab significantly improved VA compared to placebo, with a median improvement of 12.5 letters at 24 months. The RISE study followed a similar design but included patients with type 1 diabetes. The results demonstrated that ranibizumab also improved VA in patients with type 1 diabetes.

In conclusion, the treatment of DMO requires a multidisciplinary approach that includes tight glycaemic control, laser photocoagulation, and intravitreal injections. Intravitreal corticosteroids, such as the ILUVIEN implant, provide a comprehensive treatment approach, lowering the concentration of inflammatory cytokines and growth factors and improving visual outcomes in patients with DMO.

Correspondence: Thomas Bertelmann, Department of Ophthalmology, Philipps University Marburg, Baldingerstraße, 35043 Marburg, Germany. E: thomas.bertelmann@staff.uni-marburg.de

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With Clinically Significant Macular Edema (RISE and RIDE) studies evaluated the long-term efficacy and safety of ranibizumab, and data over 36 months have recently been published.33 Other anti-VEGFs with demonstrated efficacy on DMO include bevacizumab22 and pegaptanib sodium.23 However, the blockade of one single pathway may not represent an optimum treatment strategy and may explain why some patients need retreating or do not respond sufficiently.

Corticosteroids do not only have the capacity to attenuate the effects driven by overexpression of VEGF, but also reduce inflammation, and may provide a more comprehensive treatment strategy in the long-term.24 Corticosteroids reduce vascular permeability of the retina by a multifactorial process, including lowering the expression of VEGF and suppressing inflammation and leukocyte influx to the retina. The most widely used corticosteroid is triamcinolone acetonide (TA), which has shown clinical benefits in various randomised clinical trials for the treatment of DMO, and also shown improvement in VA.12,14,27 A Diabetic Retinopathy Clinical Research Network (DRCRN) study has shown that pseudophakic eyes have a comparable benefit with TA compared with ranibizumab.12,14,27 However, the use of intravitreal TA has been associated with cataracts and increased intraocular pressure (IOP).28

The administration of ocular agents for DMO is problematic.29 Topical administration does not achieve intraocular therapeutic concentrations.30 The effects of direct intravitreal injections are often short-lived and are associated with serious side effects, including cataract and elevation of IOP. Furthermore, repeated intravitreal injections impose a heavy treatment burden on patients and clinical centres and may increase the risks associated with the injection procedure, such as endophthalmitis and retinal breaks. Therefore, recent research has focused on the use of intravitreal implants. Sustained drug-delivery systems release low doses over a prolonged period, resulting in a stable and sustained intravitreal concentration of the drug thus reducing the number of injections.31 An intravitreal implant containing dexamethasone is currently in clinical development for the treatment of DMO.32

Fluocinolone acetonide (FAc) is an attractive choice for use in intravitreal implants. It is more lipophilic than TA and dexamethasone33 and therefore is expected to have superior posterior clearance with less potential for ocular side effects.34 The first steroid-containing intravitreal implant (Retisert®, not licensed in Europe) released 0.59 μg/day of FAc. A phase II study investigating the efficacy and safety of the Retisert Fac implant in 196 eyes with DMO found that VA gains of ≥15 ETDRS letters occurred in 16.8 % of implanted eyes at 6 months and 31.1 % of eyes at 3 years compared with 1.4 % at 6 months and 20 % at 3 years in the laser treatment group.35 The incidence of elevated IOP and cataract formation was much higher in eyes receiving the implant: 33.8 % required surgery for ocular hypertension and 91 % required cataract extraction by 4 years compared with 0 % and 20 % in the standard of care group (observation or laser), respectively.35

The ILUVIEN Intravitreal Implant

The ILUVIEN (Alimera Sciences) intravitreal implant is a small, cylindrical tube (3.5 mm in length; 0.37 mm in diameter) composed of an inert, non-biodegradable, polyimide material that is often used in the manufacturing of intraocular lenses (see Figure 1). The implant is injected into the vitreous cavity using a 25-gauge (nominal outer diameter 0.5144 mm) applicator, which creates a self-sealing wound (see Figure 2). It is implanted posteriorly and has a lower in vitro FAc release rate compared with Retisert, thus reducing the potential for intraocular side effects.36 Each implant contains 190 μg of FAc and, after the average initial release of 0.2 μg /day, the implant reaches a steady release that continues for up to 36 months.36 When active drug is depleted, the ILUVIEN implant is not retrieved and it remains in the eye.

The efficacy and safety of ILUVIEN has been examined in the Pharmacokinetic and Efficacy Study of Fluocinolone Acetonide Implants in Patients with DMO (FAMOUS) and Fluocinolone Acetonide for diabetic Macular Edema (FAME) clinical trials. In the open-label phase II (FAMOUS) study (n=37), a single implant provided excellent sustained intraocular release of FAc with the 0.2 μg/day FAc insert providing steady-state levels ranging between 0.5 and 1.0 ng/ml from 6 through to 36 months.37

The phase III (FAME) clinical trial comprised two randomised, double-masked, sham injection-controlled, parallel group, multicentre phase III trials performed under the same protocol. Eligibility criteria included persistent DMO (central retinal thickness [CRT] ≥250 μm and best-corrected VA (BCVA) score between 19 and 68 despite ≥1
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macular laser treatment. A total of 956 patients were randomised to sham injection (n=185), ILUVIEN implant (0.2 µg/day, n=376) or high-dose FAc implant (0.5 µg/day, n=395). At month 36, the percentage of patients who gained ≥15 ETDRS letters was 28.7 % (ILUVIEN) and 27.8 % (high-dose FAc) compared with 18.9 % (p=0.018) in the sham group. These visual gains were paralleled by a decrease in CRT.38,39

The ILUVIEN implant also demonstrated an acceptable safety profile. While most phakic patients in the implant groups developed cataract with the majority undergoing cataract surgery, their visual benefit after surgery was similar to that in pseudophakic patients.38 The incidence of incisional glaucoma surgery at month 36 was 4.8 % in the ILUVIEN group and 8.1 % in the high-dose FAc groups. Among patients treated with the ILUVIEN implant, 38.4 % required IOP-lowering medication.38,39

A preplanned subgroup analysis assessed outcomes in two groups of patients: those with a duration of DMO less than the median (<3 years) or greater than the median (≥3 years) at baseline. This analysis demonstrated a doubling of benefit in patients with chronic DMO. The percentage of chronic DMO patients who gained ≥15 ETDRS letters was 13.4 % in the sham group, 34 % in the ILUVIEN group and 28.8 % in the high-dose FAc group (p=0.018) (see Figure 3). An improvement ≥2 steps in the ETDRS retinopathy scale was reported in 13.7 % (ILUVIEN) and 10.1 % (high-dose FAc) compared with 8.9 % in the sham group.38

The findings of the FAME subgroup analysis are of particular significance, given the association between poor visual outcome and disease duration40 and the limited treatment options for patients with chronic DMO. Based on the evidence reported in the FAME studies, particularly in patients with chronic DMO, ILUVIEN has been approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of visual impairment due to chronic DMO considered insufficiently responsive to available therapies.

Clinical Experience

Two recent clinical cases of chronic DMO have described the effectiveness and safety of the ILUVIEN implant in ‘real-use’ situations in chronic DMO considered insufficiently responsive to available therapies. In both cases, the ILUVIEN implant resulted in visual gains and reductions in CRT where other therapeutic interventions had failed.

Case 1

Medical History

The patient was female, aged 71 years, with type 2 diabetes and was diagnosed with DMO on 20 June 2010. Her HbA1c was 8 % and she was receiving insulin therapy. She was pseudophakic in both eyes (OU) since 2009 and has undergone neodymium-doped yttrium aluminium garnet (Nd:YAG) posterior capsulotomy OU. Her BCVA at baseline was 0.4 in the right eye (OD) and 0.7 in the left eye (OS). Amsler grid testing was normal OS, however, metamorphopsia was documented OD.

Figure 4 shows OCT scans of both eyes together with the detailed grid for evaluating foveal thickness. The right eye shows DMO with foveal...
involvement; central foveal thickness [CFT] 448 µm); the left eye shows DMO without foveal involvement [CFT 269 µm]. Fundus photography on both eyes shows diabetic maculopathy with microaneurysms and intraretinal haemorrhages temporal to the fovea, more profoundly in the left eye (see Figure 5).

Treatment History
The patient received initial treatment with intravitreal bevacizumab in July 2010, which resulted in an improvement in BCVA from 0.4 to 0.5 OD (measured with Snellen charts) but CFT increased to 480 µm. Following the second injection of bevacizumab 2 months later, a reduction in CFT (428 µm) was seen but there was no further visual gain. The treatment was switched to TA, which resulted in further reductions in CFT (343 µm), but a slight worsening in BCVA (0.4) was observed. The patient was prescribed eye drops (dorzolamide hydrochloride, and timolol, Cosopt®) for a slightly elevated IOP (24 mmHg max) in October 2010. The patient’s IOP ranged between 15 mmHg and 23 mmHg at all subsequent follow-ups. Ranibizumab treatment, consisting of five intravitreal injections, was continued from June 2012 until April 2013 (five injections in 11 months or roughly one every 2 months) and resulted in further reductions in CFT (368 µm in June 2012, 323 µm in November 2012, 342 µm in March 2013 and 314 µm in May 2013, a reduction of 15% in 11 months) but no change in BCVA (0.5 from June 2012 to May 2013).

Response to ILUVIEN
Due to an insufficient response to ranibizumab therapy, in July 2013, the patient received an ILUVIEN implant. Within 2 months, visual gains were reported (BCVA 0.5 to 0.6), together with a reduction in CFT (314 µm to 277 µm, a 12% reduction in 2 weeks). The OCT scan taken in September 2013 illustrates the improvement in CFT (see Figure 4). To date, no adverse events or serious side effects have occurred. The IOP at last visit was below 20 mmHg despite the fact that the patient had stopped using Cosopt S as prescribed.

Case 2
Medical History
The second case was a 30 year-old patient with type 1 diabetes who was diagnosed with DMO around 20 years ago. His HbA1c was 9.5% and he was receiving insulin therapy.

Treatment History
The patient had undergone panretinal photocoagulation in both eyes, and subsequently had received 25 intravitreal ranibizumab injections OD and 12 OS since 2011. The OCT scan of the left eye taken 4 weeks after the last ranibizumab injection showed severe foveal thickening (CFT 642 µm) (see Figure 6). VA testing at this time indicated that the BCVA in this eye was 0.3.

Response to ILUVIEN
The patient received an ILUVIEN implant on 16 August 2013. There was a dramatic improvement in CFT OS (642 µm to 268 µm, a reduction of 58% in 4 weeks) (see Figure 6) and a 0.2 units improvement in BCVA from 0.3 to 0.5 4 weeks later. This improvement was sustained at 12 weeks.

Concluding Remarks
DMO is an important cause of vision loss and challenges remain in the treatment of this progressive disease. Steroids may reduce the concentration of inflammatory cytokines and growth factors such as VEGF. The efficacy and safety of the ILUVIEN implant has been demonstrated in the FAME clinical studies, and subgroup analysis has shown that the relative benefit was most substantial in patients with chronic DMO. These data have been supported by real-use clinical experience and suggest that patients with chronic DMO who are unresponsive to current therapies may respond well to the administration of an ILUVIEN implant. In conclusion, the ILUVIEN implant provides an important addition to the therapy options for patients with chronic DMO.

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