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Review

Diabetic retinopathy, a vascular and inflammatory disease: Therapeutic implications

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ABSTRACT

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes and the leading cause of visual impairment in the working-age population in the Western world. Diabetic macular oedema (DME) is one of the major complications of DR. Therapy with intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) drugs has become the gold standard treatment for DR and its complications. However, these drugs have no effect on the pathogenesis of DR and must be administered frequently via invasive intravitreal injections over many years. Thus, there is a pressing need to develop new therapeutic strategies to improve the treatment of this devastating disease. Indeed, an increasing volume of data supports the role of the inflammatory process in the pathogenesis of DR itself and its complications, including both increased retinal vascular permeability and neovascularization. Inflammation may also contribute to retinal neurodegeneration. Evidence that low-grade inflammation plays a critical role in the pathogenesis of DME has opened up new pathways and targets for the development of improved treatments. Anti-inflammatory compounds such as intravitreal glucocorticoids, topical non-steroidal anti-inflammatory drugs (NSAIDs), antioxidants, inflammatory molecule inhibitors, renin–angiotensin system (RAS) blockers and natural anti-inflammatory therapies may all be considered to reduce the rate of administration of antineovascularization agents in the treatment of DR. This report describes the current state of knowledge of the potential role of anti-inflammatory drugs in controlling the onset and evolution of DR and DME.

Introduction

Diabetes is the most prevalent worldwide metabolic disease and a growing global problem [1]. Diabetic retinopathy (DR) is the most common microvascular complication of diabetes and, several years after its onset, leads to the development of macular oedema (DME), one of the major complications of DR and the leading cause of visual impairment in the working-age population in the Western world [1].

Chronic hyperglycaemia exerts its toxic effects by activating various metabolic pathways that induce oxidative damage to the walls of retinal capillaries, causing their occlusion. Hyperglycaemia activates, from its early stages, transcription factors that upregulate proinflammatory molecules, thereby creating low-grade inflammation in the retina and triggering the activation of microglial cells [2–4].

The endothelium of the diabetic retina increases expression of intercellular adhesion molecule (ICAM)-1, with a consequent accumulation of leucocytes around the vascular walls of retinal capillaries that, in turn, releases cytokines, chemokines, and proinflammatory and pro-angiogenic growth factors in the retina, resulting in a low-grade inflammatory state. Inflammatory mediators disrupt the tight junctions between endothelial cells and increase vascular permeability, triggering breakdown of the blood–retinal barrier (BRB) and the onset of intraretinal oedema.

Abbreviations: DR, diabetic retinopathy; DME, diabetic macula oedema; NSAIDs, non-steroidal anti-inflammatory drugs; ICAM-1, intracellular adhesion molecule-1; BRB, blood–retinal barrier; HSP, heat-shock protein; TA, triamcinolone acetonide; MMP, matrix metalloproteinase; MAPK, mitogen-activated protein kinase; BFGF, basic fibroblast growth factor; NF-κB, nuclear factor kappa B; TNF, tumour necrosis factor; AP-1, activator protein 1; TGF, transforming growth factor; IL, interleukin; IVTA, intravitreal administration of triamcinolone acetonide; BCVA, best correct visual acuity; COX, cyclooxygenase; iNOS, inducibile nitric oxide synthase; PG, prostaglandin; ROS, reactive oxygen species; RAS, renin–angiotensin system; ACE, angiotensin-converting enzyme; AT1R, angiotensin II type 1 receptor.

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Such low-grade proinflammatory activity increases the toxicity of chronic hyperglycaemia by damaging pericytes around endothelial cells and weakening the walls of the endothelial network through intraretinal serum leakage. The increasing extracellular hydrostatic pressure facilitates the further collapse and occlusion of the capillary network, so increasing retinal ischaemia. The death of pericytes, disruption of tight junctions, and glycosylation and thickening of the endothelial basal membrane trigger the development of vascular abnormalities, such as microaneurysms, vascular loops, venous beading, and erosions and enlargements of the foveal avascular zone, all of which form the basis of DR (Fig. 1) [2].

Vascular hyperpermeability and ischaemia in the macular area lead to the onset of DME. When ischaemia affects large areas of retina, inflammation can trigger and drive the neovascular proliferation that spreads from the retinal arcades and papilla to the posterior hyaloid [4,5]. In addition, inflammation contributes to the retinal neurodegeneration associated with diabetes [4,6,7].

Many studies have shown a significant increase in levels of inflammatory cytokines, chemokines and other factors in the ocular fluid of diabetes patients [2,4,8–16]. Analysis of vitreous fluid obtained from either diabetes patients undergoing vitrectomy or diabetic donors has led to the identification of a number of intraocular mediators that may be involved in the pathogenesis of DR, and which potentially could be targeted by future therapeutic strategies [11].

At present, primary prevention with intensive glycaemic control, strict blood pressure regulation and lipid-modifying therapy remain the top goals in managing patients with diabetes. Intensive systemic diabetes management is able to delay the onset of DR and slow its progression, and is particularly effective in patients with mild DR [17]. Nevertheless, once it arises, DR often self-maintains and worsens on its own. Grid, focal or panretinal photocoagulation laser treatment has been the most effective tool for slowing the progression of DR for the last 30 years [18,19]. However, these ocular therapies have significant side effects and have limited effectiveness in improving visual acuity.

In recent years, the use of therapy based on intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) drugs has become the first-line treatment for DR [19]. Many controlled clinical trials have demonstrated that these therapies are more effective for improving visual acuity than laser treatment alone. However, these drugs have no effect on the pathogenesis of DR and must be invasively administered almost every month for at least a year before their frequency of use can be reduced. Anti-VEGF therapies are also costly, as they are associated with a considerable financial commitment for the clinical institution as well as significant discomfort for patients due to the numerous invasive administrations they have to undergo.

However, evidence of the role of inflammation in the pathogenesis of DR has provided new pathways and targets for novel and customized treatments. Thus, the present report describes our current knowledge of the potential role of anti-inflammatory drugs (Table 1) in controlling the evolution and onset of DR and DME.

Corticosteroids

These agents reduce inflammation via two mechanisms:

- an intracellular (genomic) pathway that acts through direct interaction with deoxyribonucleic acid (DNA) activity;
- an extracellular (non-genomic) pathway that influences vessel activity and Müller cells [20].

Corticosteroid molecules are transported in serum by a corticosteroid-binding protein (CBG) that, when it comes into contact with cell membranes, crosses into the cytoplasm, where it binds with a glucocorticoid receptor expressed by a group of heat-shock proteins (Hsp90) that allow the corticosteroid molecules to penetrate into the cell nucleus. In the nucleus, CBG binds with different genes that are either activated or deactivated in the production of their respective proteins through production of specific messenger ribonucleic acids (mRNAs). Thus, corticosteroids are able to interact with cellular metabolism and the inflammatory pathway, affecting the production of more than 600 proteins [21].

The main effects of corticosteroids in the eye include reestablishment of the disrupted BRB and downregulation of proinflammatory markers. The extracellular mechanism works via a direct influence on the cytoplasmic membrane of vessels (reducing permeability and inducing vasoconstriction) and Müller cells (reducing cellular swelling and inducing adenosine production). Their vasoconstrictive actions and effect on Müller cells contribute to reabsorption of fluid, thereby reducing DME [21–23]. Different intracellular mechanisms of action (genomic and non-genomic) may either up- or downregulate a number of other enzymes and cytokines, with variable metabolic effects. Corticosteroids also restore tight junction integrity by stabilizing blood–ocular barrier

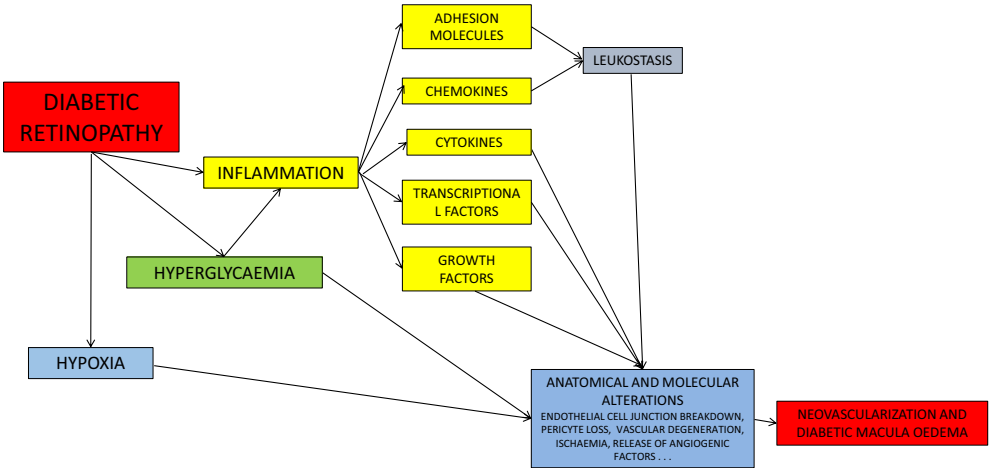

Fig. 1. The pathogenesis of diabetic retinopathy.

Table 1
Anti-inflammatory therapies for diabetic retinopathy (DR).

Drug category	Mechanism	Target	Effect on DR	Effects on DME
Corticosteroids [20–67]	Proinflammatory transcription factor blockade	Glucocorticoid receptor	Prevent ICAM-1 expression, leukostasis, vascular leakage	Prevent ICAM-1 expression, leukostasis, vascular leakage; improve visual acuity, decrease macular thickness
Non-steroidal anti-inflammatory drugs (NSAIDs) [68–98]	Inhibition of proinflammatory molecules, prostaglandin production	COX	Prevent ICAM-1 expression, leukostasis, vascular leakage, capillary cell apoptosis, vessel degeneration; reduce incidence of DR, development of retinal microaneurysms	Prevent ICAM-1 expression, leukostasis, vascular leakage, capillary cell apoptosis, vessel degeneration
Antioxidants [99–105]	Antioxidative stress	Oxidative stress	Reduce vessel degeneration; reverse some changes in retinal vessels	Reduce vessel permeability
Inflammatory molecule inhibitors [106–121]	Blocking of TNF-α-induced inflammation	TNF-α	Reduce proangiogenetic stimuli	Improve visual acuity; reduce macular thickness
Renin–angiotensin system (RAS) blockers [122–127]	Blocking of RAS-mediated inflammation	RAS	Prevent oxidative stress, inflammation, vascular damage; reduce risk & progression of retinopathy	Prevent oxidative stress, inflammation, vascular damage
Natural anti-inflammatory therapies [128–148]	Antioxidative, anti-inflammatory, antiproliferative properties	VEGF, TNF, ICAM-1…	Prevent cell degeneration, prevent oxidative stress, inhibit angiogenesis, enhance immune defence	Prevent cell degeneration, oxidative stress

DME: diabetic macular oedema; ICAM-1: intercellular adhesion molecule-1; COX: cyclooxygenase; TNF-α: tumour necrosis factor-alpha; VEGF: vascular endothelial growth factor.

functions, which reduces both serum leakage and expression of extracellular matrix metalloproteinase (MMP) [24].

Triamcinolone acetonide (TA) is a potent glucocorticoid shown to inhibit the positive feedback regulation between VEGF and MMP-9 under hypoxic conditions by inhibiting expression of the *MMP-9* gene and VEGF secretion [25]. In addition, glucocorticoids inhibit prostaglandin production through several independent mechanisms: induction and activation of annexin 1 (also called lipocortin 1); induction of mitogen-activated protein kinase 1 (MAPK1); and transcriptional repression of cyclooxygenase 2 (COX-2). Several studies have demonstrated that corticosteroids attenuate the expression of adhesion molecules related to leukostasis, and inhibit the release and secretion of inflammatory cells (leucocytes, monocytes, macrophages). Penfold et al. [26,27] demonstrated that TA downregulates expression of intercellular adhesion molecules (ICAMs) such as ICAM-1 and E-selectin, and other proteins related to inflammation, such as interleukin (IL)-6 protein, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), tumour necrosis factor (TNF)-α, activator protein (AP)-1 and interferon (IFN)-γ [28].

In addition to their anti-inflammatory effects, glucocorticoids also have an angiostatic effect useful in the treatment of DR. This effect was discovered by studies showing that these compounds inhibit laser-induced choroidal neovascularization (CNV) in the eyes of animal models [28–31]. Indeed, both animal studies and experimental models have demonstrated that most of the proangiogenesis mediators that stimulate neovascularization, including VEGF, basic fibroblast growth factor (BFGF), transforming growth factor (TGF)-β and IL-6, are inhibited by exposure to glucocorticoids [32].

Experiments in vitro have demonstrated that corticosteroids can also modulate vascular permeability by suppressing production of VEGF mRNA, VEGF-mediated protein expression, and VEGF receptors in human cell cultures, macrophages and endothelial cells [33]. Studies in vivo have demonstrated that TA strongly inhibits VEGF and stromal cell-derived factor (SDF)-1 levels within the vitreous as well [34]. In addition, studies using immunohistochemical staining have reported that TA appears to exert its angiogenesis inhibitory effects on CNV by enhancing endostatin expression [35]. Moreover, the anti-inflammatory effects of corticosteroids indirectly suppress the hypoxia-induced expression of VEGF by retinal pigment epithelial cells [36]. Finally, long-term steroid use may have an additional neuroprotective effect on the retina [37].

However, the use of systemic steroids to treat DME is not recommended due to systemic side effects such as worsening diabetes [22], although they can be administered intravitreally. Indeed, preclinical and clinical studies have shown the beneficial effects of intravitreally injected steroids for DR. The first clinical evidence of intravitreal corticosteroid efficacy in reducing bleeding and postoperative oedema involved dexamethasone sodium phosphate injected after vitreoretinal surgery for DR [38]. Before the advent of anti-VEGF drugs, many scientific studies had shown the usefulness of intravitreal steroids in reducing the occurrence of DME, especially in cases refractory to laser photocoagulation. Moreover, even after the advent of anti-VEGF drugs, corticosteroids proved to be useful in the treatment of DME, as they act on mediators not influenced by anti-VEGF treatment.

One recent study compared changes in aqueous levels of the inflammatory cytokines IL-6, IL-8, IFN-γ-induced protein 10 (IP-10), monocyte chemoattractant protein (MCP)-1 and platelet-derived growth factor (PDGF), and of angiogenic cytokines (VEGF) after intravitreal injections of TA and bevacizumab in patients with DME. Levels of IL-6, IP-10, MCP-1, PDGF-AA and VEGF significantly decreased in TA-treated eyes, whereas only VEGF levels decreased in eyes treated with bevacizumab [39]. Thus, the combined use of steroids (which target inflammatory cytokines) and anti-VEGF (which target the VEGF molecule) in the treatment of DME appears to have more comprehensive and durable effects than anti-VEGF alone [40].

In fact, intravitreal steroid administration has proved to be a fundamental alternative to anti-VEGF drugs in treatment-naïve eyes affected by DME. It is also useful for reducing the frequency of anti-VEGF intravitreal injections in patients with coronary diseases, for whom anti-VEGF agents are contraindicated [40]. Corticosteroids available for intravitreal use include TA, dexamethasone sodium phosphate and fluocinolone acetonide.

Triamcinolone acetonide

TA is a synthetic corticosteroid (C24H31FO6) with a molecular weight of 434.50 Da. Its anti-inflammatory activity depends on the integrity of its 21-hydroxyl group. TA used in ophthalmology is

available as an injectable suspension, a water-insoluble particulate drug comprising steroid crystals that can remain in the vitreous cavity for a longer period of time, and thus may have a longer duration of action, after intravitreal injection than other corticosteroids that disappear within a matter of days. The most commonly used TA brand is Kenalog-40 (Bristol-Meyers Squibb, New York, NY, USA); other trade names include Aristocort, Azmacort, Kenacort-A, Ledercort, Omcilon A, Tricortone and Trianex. Recently, the US Food and Drug Administration (FDA) approved Trivaris (8 mg/0.1 mL; Allergan, Inc., Dublin, Ireland) and Triesence (4 mg/0.1 mL; Alcon Laboratories, Inc., Geneva, Switzerland) specifically for ophthalmic use. In 2013, the Agenzia Italiana del Farmaco (AIFA; Italian Medicines Agency) approved the use of Taioftal [4 mg/0.1 mL, SOOFT Italia, Fidia Farmaceutici SpA, Abano Terme (PD), Italy] for DME treatment. These three products are free of preservatives and suitable for intravitreal injections.

Intravitreal TA (IVTA) is not significantly absorbed into the systemic circulation after administration, as the particulate drug accumulates in the inferior vitreous gel, although persistence of the steroid crystals in the posterior chamber depends on the dose and integrity of the vitreous fibrillar structure. In patients with a liquefied vitreous (in highly myopic or vitrectomized eyes) or with aphakic and pseudophakic eyes, TA dissolution is quicker whereas, in patients with a compact vitreous and adherent vitreous cortex, TA crystal dissolution is slower. A 4-mg dose of TA in a non-vitrectomized human eye maintains measurable concentrations for around 3 months [41]. Vitreous TA concentration after 4-mg IVTA was 1.22 ± 0.24 μg/mL, which is significantly higher than after sub-Tenon injection (< 0.001 μg/mL), while a 25-mg dose of TA was reported to remain in the vitreous and aqueous humour for up to 6 months after injection [42].

IVTA has been assessed in numerous clinical and preclinical studies of DR and other ocular neovascular diseases [41,43]. In DR patients, it leads to regression of macular oedema and neovascularization, with associated reductions in levels of VEGF and SDF-1 [44]. IVTA treatment has also resulted in improved visual acuity in several case series [45,46]. However, the potent acute effect of TA *vs* the longer but slower effect of laser photocoagulation suggests that combination therapy may be the best option. In a randomized clinical trial of 69 eyes with DME refractory to laser treatment, Gillies et al. [20] showed that IVTA in combination with laser coagulation improved visual acuity and decreased central macular thickness more than with laser photocoagulation alone. After a 2-year follow-up, visual improvement (five letters) was noted in 56% of treated eyes (vs. 26% of controls); however, cataract development was observed in 54% of treated eyes (vs. 0% of controls).

The Diabetic Retinopathy Clinical Research Network (DRCR.net), a collaborative network to facilitate multicentre clinical research into DR, was established in 2002 by the US National Eye Institute. The DRCR.net protocol B involved subjects with DME (840 eyes) randomized to receive focal/grid laser therapy, 1-mg IVTA or 4-mg IVTA every 4 months if necessary. At 4 months, the mean best corrected visual acuity (BCVA) was better in the 4-mg IVTA group than in either the laser or 1-mg IVTA groups. However, at the end of 12 months, none of the three treatments were significantly different in terms of mean BCVA. In fact, after 16 months and at the end of the 3-year follow-up, mean BCVA and retinal thickness were better in the laser group than in either of the two IVTA groups [47,48]. On the other hand, IVTA appeared to reduce the risk of DR progression [49].

Thus, while the study confirmed the short-term efficacy of treatment with IVTA, in the long-term, laser photocoagulation was superior and had fewer side effects which, with IVTA, consisted mainly of cataracts and elevated intraocular pressure (IOP). The majority of patients in both IVTA groups developed cataracts (46% and 83% vs. 31% of controls), while an increased IOP requiring therapy was recorded in a significant number of IVTA patients (16–33% vs. 4% of controls). In addition, endophthalmitis appears to be a rare side effect related to the use of IVTA [50,51].

To provide data on the safety and efficacy of sub-Tenon injection of TA either alone or in combination with photocoagulation for mild DME, the DRCR.net also conducted a study (protocol E) of 129 eyes. Although findings suggested that a greater proportion of eyes had a reduction (250 μ) in central subfield thickness when peribulbar TA was combined with focal photocoagulation, the difference was not statistically significant. Thus, the trial concluded that this form of administration is unlikely to be of substantial benefit [52].

IVTA has proved to be an effective, short-term option for treating proliferative DR, with treatment effects lasting for only around 6 months, such that repeated administration may be required [53]. However, the DRCR.net Protocol J study showed that the addition of one IVTA or two ranibizumab injections in eyes receiving laser panretinal photocoagulation for proliferative DR reduced the risk of DME exacerbation and associated visual acuity loss [54,55].

The DRCR.net study using Protocol I randomized 691 patients (854 eyes) with DME involving the fovea into four groups: sham injection and prompt laser treatment; 0.5-mg ranibizumab and prompt laser treatment; 0.5-mg ranibizumab and deferred ($\geq$ 24 weeks) laser treatment; and 4-mg IVTA and prompt laser treatment. After 1 year, treatment with IVTA + laser resulted in a gain of four letters from baseline, compared with a three-letter gain in the laser-only group and a nine-letter gain in both ranibizumab + laser groups. Also, in a subgroup of pseudophakic patients treated with IVTA + laser, BCVA gain was comparable to that of pseudophakic eyes treated with ranibizumab + laser and superior to that with laser treatment only. However, IOP elevation and cataract surgery were more frequent in the IVTA group, although the number of IV injections (3 vs. 12 per year) and total cost of treatment were significantly lower [52].

Dexamethasone sodium phosphate

This was the first glucocorticoid agent to be injected into the vitreous to treat DR [38]. IV injection of dexamethasone in the same way as IVTA significantly decreased inflammatory processes, thereby alleviating BRB breakdown, reducing upregulation of ICAM-1, reducing leukostasis and preventing retinal vascular leakage in rat retinas [56]. Dexamethasone also appears to induce fewer side effects, such as increased IOP and cataracts, compared with TA. However, because of its water solubility, it remains in the vitreous for only a few weeks.

Ozurdex® (Allergan), an IV implant that releases dexamethasone, was recently approved by the US FDA for treatment of macular oedema secondary to retinal vein occlusion, non-infectious uveitis and DME. This biodegradable implant, which uses a NOVADUR™ delivery system, consists of 0.7 mg of dexamethasone and poly(D,L-lactide-co-glycolide) matrix microspheres. In the vitreous, these microspheres are slowly degraded into lactic and glycolic acids, thereby allowing the gradual release of dexamethasone over 6 months. After this time, no trace of the implant remains within the eye [57].

Callanan et al. [58] first evaluated dexamethasone as a treatment for DME in the PLACID trial. Patients with DME involving the fovea were randomized at month 1 to either 0.7-mg Ozurdex implant + laser therapy or laser monotherapy with a sham implant injection. Subjects could receive up to three additional laser treatments and one additional Ozurdex injection. Although there was no difference between the groups at 1 year, the percentage of patients gaining at least 10 letters on BCVA was

significantly higher in the Ozurdex + laser than in the laser monotherapy group at both months 1 and 9. However, an increased IOP was more frequently observed in the Ozurdex + laser group, although no eyes required surgery to control it. In addition, cataract-related adverse events were more common among phakic patients in the Ozurdex + laser than laser monotherapy group.

In the Ozurdex MEAD Study Group trials, two large double-blind studies to evaluate Ozurdex for DME, a total of 1048 eyes with DME and central retinal thicknesses (CRT) $\geq$ 300 μm were randomized to receive either 0.7-mg Ozurdex, 0.35-mg Ozurdex or a sham procedure. Repeat treatment with Ozurdex was allowed, but no more than every 6 months. At the end of the 3-year follow-up, the percentage of patients gaining $\geq$ 15 letters was significantly higher in both dexamethasone groups than in the sham control group (22.2% and 18.4% in the 0.7-mg and 0.35-mg Ozurdex groups, respectively, vs. 12% in the sham group); the percentage of patients with an increase of IOP $\geq$ 10 mmHg was 27.7% and 24.8% with Ozurdex, respectively, vs. 13% of the controls. IOP $\geq$ 35 mmHg was observed in 6.6% and 5.2% of patients receiving Ozurdex, respectively, vs. 0.9% of the controls. Antiglaucoma treatment was required for 41.5% and 37.6% of the Ozurdex groups, respectively, vs. 9.1% of the controls. Two patients in the Ozurdex groups had to undergo glaucoma surgery, while cataract development was evident in 67.9% and 64.1% of the Ozurdex groups, respectively, and in 20.4% of the controls [59]. Currently, Ozurdex is indicated for the treatment of visual impairment due to DME in patients who have already undergone cataract surgery, or in those considered to have an insufficient response or are unable to undergo other types of treatment.

In the uncontrolled study by the CHAMPLAIN Study Group, Ozurde × 0.7 mg proved useful in the treatment of DME in patients who underwent pars plana vitrectomy (PPV). After 8 weeks, macular oedema decreased by an average of 156 μ and visual acuity increased by 10 letters in 30.4% of patients. No patient required surgery to control IOP despite a significant IOP increase reported in 16% of patients [60].

Fluocinolone acetonide

Iluvien® (Alimera Sciences, Alpharetta, GA, USA) is a non-biodegradable implant inserted in the vitreous cavity by needle that allows the slow steady release of fluocinolone acetonide (FA) for up to 3 years. This glucocorticoid has lower lipophilicity than TA (or dexamethasone) and, therefore, has less diffusion in the aqueous humour and fewer IOP side effects. Iluvien is a miniature 3.5 × 0.37 mm cylindrical insert injected into the vitreous chamber via a 25-gauge needle [61,62].

The fluocinolone acetonide in diabetic macular edema (FAME) A and B were two methodologically identical parallel studies designed to assess whether IVFA was safe and effective in the treatment of DME [61,63–65]. These trials enrolled a total of 956 patients with central DME, BCVA of 20/50 to 20/200 and CRT $\geq$ 250 μm who were randomized into three groups: low dose at 0.23 μg/day; high dose at 0.45 μg/day; and sham injection. Additional treatment was provided after 1 year based on predefined re-treatment criteria. At month 36, mean improvement in BCVA letters from baseline was 8.1 (0.23 μg/day dose) and 7.1 (0.45 μg/day) compared with 3.1 in the sham control group (P = 0.007). A final BCVA of $>$ 20/40 was attained at month 36 in 35% and 34.9% of patients with the FA implants compared with 26.5% of the controls. Also, at month 24, mean foveal thickness was significantly lower in the implant groups (low dose: 293 μm; high dose: 308 μm) vs. the sham group (340 μm) [65].

Further analyses showed that this treatment was more effective in eyes with chronic DME ($\geq$ 3 years from diagnosis) than in those with acute DME: 34% of patients with chronic DME gained 15 letters vs. 22.3% of patients with acute DME. The risk–benefit ratio was better in the low-dose group (0.23 μg/day) which had a need for glaucoma surgery in 3.7% vs. 7.6% of those treated with a high dose (vs. 0.5% in the sham group). The need for cataract surgery affected 41.1% of patients treated with the low dose and 50.9% of those in the high-dose group (vs. 7% in the sham group) [66].

Iluvien was approved by the FDA in September 2014 for the treatment of DME in patients previously treated with corticosteroids with no clinically significant rise in IOP. Iluvien had already been approved by the European Medicines Agency (EMA) in April 2014 for the treatment of chronic DME not sufficiently responsive to other available therapies. The approved dose is 0.19 mg, which provides sustained delivery in the eye for at least 1 year, after which the implant may be repeated [67].

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are among the most prescribed drugs, and are commonly used for their analgesic, antipyretic and anti-inflammatory properties. They are inhibitors of COX enzymes, and reduce the synthesis of proinflammatory prostaglandins (PGs). COX-1 is important for homoeostasis processes and is expressed constitutively in many cell types, whereas COX-2 is produced mainly at sites of inflammation, and predominantly induces synthesis of proinflammatory PGs such as PGE2 and PGF2α [68]. Inducible nitric oxide synthase (iNOS) and COX-2 are often expressed during inflammation [6], as both are influenced by NF-κB activity [69]. Products of iNOS positively regulate COX-2 expression and activity [69]. COX-2 expression and its products (such as PGE2) are significantly elevated in the retinas of diabetic animals and in retinal cells treated with high levels of glucose [70,71], while inhibition of COX-2 reduces the production of PGE2 in diabetic rat retinas [72], and blocks diabetes-induced ICAM-1 expression and leukostasis [70,73,74]. For these reasons, COX-2 could play a role in retinal inflammation, while NSAIDs may have therapeutic potential in DR [6].

In ophthalmology, topical NSAIDs are mainly used to stabilize pupil dilation during intraocular surgery to control postoperative pain and inflammation (particularly after refractive surgery), and to treat allergic conjunctivitis and cystoid macular oedema [75]. An increasing number of studies suggest that NSAIDs may also have positive effects in DR, ocular cancers and senile macular degeneration [76–81]. Aspirin treatment prevents capillary cell apoptosis and vessel degeneration in diabetic animals [82–84]. Specific COX-2 inhibitors reduce vascular leakage, capillary cell apoptosis and vessel degeneration [73,85,86].

In 1964, researchers observed that rheumatoid arthritis patients chronically treated with salicylates had a reduced incidence of DR [87]. This was further investigated in two clinical trials: the Early Treatment Diabetic Retinopathy Study (ETDRS), which examined the effects of systemic administration of 650 mg of aspirin to patients with advanced DR; and the Dipyridamole Aspirin Microangiopathy of Diabetes (DAMAD) study, which assessed the effects of systemic administration of 990 mg of aspirin in patients with early DR [88]. While no benefits were observed in the ETDRS, which involved patients with advanced DR, significant benefits were reported in the DAMAD study, in which higher doses of aspirin were effective in slowing the formation of microaneurysms. This observation has been further confirmed by a recent prospective study in which NSAID treatment prevented DR development and progression [89].

However, clinical trials of specific COX-2 inhibitors have been discouraged due to the increased risk of heart attack and stroke posed by systemic COX-2 inhibitors [21] and, in preclinical studies, topical administration of a COX-2 inhibitor was found to reduce DR symptoms similarly to systemic administration [6,85,86]. Topical NSAIDs administered to eyes are absorbed by the nasolacrimal system and mucous membrane surface, and reach therapeutic levels in the aqueous humour, thereby reducing the synthesis of PGs in the ciliary body and iris, an effect that is less evident in the retina and choroid. Yet, few studies have measured NSAID levels in the human vitreous after topical administration. Russo et al. [90] measured vitreous concentrations of 0.5% indomethacin, 0.9% bromfenac and 0.1% nepafenac following topical administration for 7 days before vitrectomy in patients with macular pucker or vitreomacular adhesion, and reported concentrations of 503.13 ± 241.1 g/mL, 302.5 ± 91.03 g/mL and 284.38 ± 128.2 g/mL, respectively, while PGE2 vs. placebo reductions were 78%, 72% and 60%, respectively; these values were all statistically significant.

Heier et al. [91] measured vitreous concentrations of 0.4% ketorolac, 0.09% bromfenac and 0.1% nepafenac (amfenac) administered for 3 days prior to vitrectomy, and found levels of 2.8 ng/mL for ketorolac, 0.96 ng/mL for bromfenac and 2.0 ng/mL for amfenac. Only ketorolac significantly reduced IV concentrations of PGE2 compared with placebo despite being primarily a COX-1 inhibitor (unlike bromfenac and nepafenac/amfenac, which mostly inhibit COX-2). These results were confirmed by Schoenberger et al. [92], who measured IV concentrations of ketorolac and PGE2 in patients with macular holes, macular puckers and vitreous opacity following topical administration of ketorolac four times a day for 3 days prior to vitrectomy.

The effect of ketorolac on aqueous humour was also studied by Bucci et al. [93], who administered ketorolac (four times daily) and bromfenac (twice daily) for 2 days before phacoemulsification. After measuring aqueous humour concentrations of these two NSAIDs and of PGE2, they found that concentrations of ketorolac were significantly higher than those of bromfenac. Moreover, ketorolac achieved a greater reduction of PGE2 concentration than bromfenac.

Russo et al. [80] found that topical administration of ketorolac in combination with IV anti-VEGF injections in patients with senile macular degeneration significantly reduced macular central thickness after 6 months, although there were no differences in either visual acuity or number of injections between the two groups. In contrast, Gomi et al. [78] reported no reduction in frequency of ranizumab injections combined with topical bromfenac.

Similar results were recently described in a trial in which the efficacy of combined treatment with ranizumab + bromfenac was compared with ranizumab treatment alone in patients with senile macular degeneration. After 12 months, a significant reduction of central macular thickness was observed in patients treated with the combination *vs* those treated with ranizumab alone (−28.3% vs. −18.9%, respectively). However, there were no differences in visual acuity between the two groups. These results contrast with those of two previous retrospective studies of patients with senile macular degeneration in which no improvement in either visual acuity or macular thickness was detected after the addition of either bromfenac or nepafenac administered concomitantly with anti-VEGF drugs [94,95].

Pinna et al. [96] found that topical administration of bromfenac in diabetes patients with DME reduced macular thickness after 30 days of treatment. Schoenberger et al. [97] conducted a study showing that administration of 0.45% ketorolac to DR patients four times a day for 3 days prior to vitrectomy significantly reduced aqueous concentrations of IL-8 (52% reduction vs. placebo; $P = 0.04$). In addition, they also found that 0.45% ketorolac led to significant reductions in vitreous IL-8 (41% reduction vs. placebo; $P = 0.002$) and PDGF-AA (21% reduction vs. placebo; $P = 0.009$), suggesting that this NSAID may result in significant inhibition of the inflammatory cytokines involved in the pathogenesis of diabetes.

Medić et al. [98] found that 0.1% diclofenac administered topically four times a day for 7 days before and 30 days after surgery in non-proliferative DR patients resulted in decreased concentrations of IL-12 in the aqueous humour. They also documented a reduction in central macular thickness after phacoemulsification in these diclofenac-treated patients.

These data suggest that pre- and postoperative therapy with topical NSAIDs can reduce the incidence of macular oedema following phacoemulsification in DR patients. However, these studies had mixed results that could have been due to differences in study parameters, such as including patients with different ocular pathologies, small sample sizes and different durations of retrospective studies, thereby making direct comparisons of these data particularly complex. Thus, it would be helpful to further investigate the therapeutic benefits of NSAIDs in additional clinical trials.

Antioxidants

In diabetes, elevated levels of reactive oxygen species (ROS) are generated by both vascular endothelium and leucocytes adherent to endothelium in certain regions of the retina, leading to an impaired antioxidant defence system and, thus, an increase in oxidative damage [99]. Oxidative stress is an important target for anti-inflammatory therapy, and blocking oxidative stress may be a useful approach in treating DR. In preclinical studies, antioxidants (such as vitamins C and E) were shown to attenuate the development of acellular capillaries and to decrease the number of pericyte ghosts [100]. However, clinical studies have given contrasting results. One found that vitamin E reversed some changes in the retinal vessels of diabetes patients [101], whereas another found that antioxidant therapy resulted in no beneficial effects [102]. Thus, it seems necessary to target specific dysregulated mechanisms generating oxidative stress while avoiding interfering with the physiological roles of ROS [6].

In preclinical studies, blocking the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity induced by diabetes prevented vascular leakage and neovascularization [103]. The data reveal that NADPH plays a critical role in retinal inflammatory reactions and vascular leakage [6,18]: NADPH oxidase blockers might prevent the C-C motif chemokine ligand 2 (CCL2) production induced by various inflammatory stimuli in retinal cells [104]. This pathway regulates the production of CCL2 via activation of NF-κB. In retinal cells treated with high levels of glucose, NADPH oxidase inhibition significantly inhibited oxidative stress, NF-κB activation, ROS formation and inflammatory reactions [105].

Inflammatory molecule inhibitors

Several studies have investigated whether targeting specific inflammatory molecules is of value in DR treatment [6,18]. The proinflammatory cytokine TNF-α has been implicated in a number of inflammatory diseases, including DR [106]. It binds to TNF-α receptors 1 and 2 localized on the cell surface, and induces ROS formation, NF-κB activation, iNOS expression in inflammatory cells, and upregulated expression of adhesion molecules such as E-selectin, vascular cell adhesion molecule (VCAM)-1 and ICAM-1 at the endothelial surface [90]. TNF-α levels are significantly increased in DR [85,107,108], although the effect of anti-TNF-α

therapy on DR has only been studied in animal models of diabetes and a few clinical cases [6]. Etanercept is a recombinant fusion protein having anti-TNF-α properties, and is FDA-approved for the treatment of psoriasis [109]. A small series of patients with refractory DME were treated with IV etanercept, but no statistically significant improvement was observed [110].

Infliximab, a monoclonal antibody directed against TNF-α, is used to treat Crohn's disease. Sfikakis et al. [111] administered it to four patients with DME non-responsive to laser photocoagulation. After 2 months of 5 mg/kg intravenous (IV) infliximab, five of the seven symptomatic eyes showed positive responses, including improvement in visual acuity and reduction in macular thickness, with further improvement seen after repeated infusions. Similar results were also observed using systemic infliximab to treat age-related macular degeneration [112]. However, iv infliximab at similar doses (3–5 mg/kg) led to a high incidence of serious adverse events [113,114]. One possible approach to minimize these concerns is to formulate the antibody for IV injection, thereby allowing a dramatically reduced dosing schedule, as seen with VEGF-targeted reagents. In addition, given the apparent independence of VEGF and TNF-α in mediating DR-associated inflammation, combination approaches may be effective as well [115].

When canakinumab (Novartis, Basel, Switzerland), a selective IL-1β antibody for treating patients with proliferative DR that leads to stabilization, but not regression of retinal neovascularization despite promising reducing effects on diabetes-related macular oedema [116], and an oral inhibitor targeting MCP-1 and CCR2/CCR5 receptors (Pfizer, New York, NY, USA) were compared with IV anti-VEGF therapy in DME patients, the study drug showed non-inferiority in terms of visual acuity gains and reduced central retinal thickness [17,117].

Leukostasis, as already mentioned, is involved in the pathogenesis of DR. An integrin expressed in leucocytes—leucocyte function-associated antigen (LFA)-1—is important in the leucocyte–endothelial cell interaction as it binds to ICAM. One study showed that topical delivery of SAR 1118, an antagonist of LFA-1, decreased leukostasis and retinal vascular leakage in a diabetic rat model [118]. Leukostasis involves interactions between very late antigen (VLA)-4 on leucocyte plasma membranes and VCAM-1 on endothelial cells. Blocking VLA-4 with anti-CD49a, part of the molecular neutralizing antibody, significantly attenuates diabetes-induced leukostasis and vascular leakage [119]. Moreover, the anti-CD49a neutralizing antibody reduces NF-κB activity and protein levels of VEGF and TNF-α, indicating that leucocyte recruitment has a positive feedback role in the DR inflammatory pathway [6]. The DEL MAR Phase-2b trial using the integrin antagonist Luminate® (ALG-1001; Allegro Ophthalmics LLC, San Juan Capistrano, CA, USA) as sequential therapy to a single anti-VEGF injection in DME patients compared with anti-VEGF monotherapy reported sustained and equal visual acuity gains with both treatments [17,120].

Advanced glycation end product (AGE) and receptor for advanced glycation end product (RAGE) pathways are important mechanisms in retinal inflammation, and could be an emerging target for DR [6]. Studies have shown that blocking this axis with soluble RAGE or inhibiting AGE formation improves neuronal function, and limits the development of acellular capillaries and pericyte loss in diabetic mice [121].

Renin–angiotensin system (RAS) blockers

The RAS could be a target for DR treatment as it is involved in retinal inflammation in diabetes. This pathway interferes with numerous other pathways, including the oxidative stress and AGE pathways [6]. Angiotensin II type 1 receptor (AT1R) blockers (losartan, candesartan) and angiotensin-converting enzyme (ACE) inhibitors (enalapril) have been shown to prevent oxidative stress, inflammation and vascular damage, and to reduce the risk of DR and its progression in animal models of diabetes [122,123].

Several clinical trials have aimed to evaluate whether RAS interventions can slow the progression of DR. Mauer et al. [124] demonstrated slowed progression of DR by RAS blockade with losartan (an AT1R blocker) and enalapril (an ACE inhibitor). However, this benefit was not observed in the Diabetic Retinopathy Candesartan Trials (DIRECT), which showed that candesartan treatment reduced the incidence of DR, but did not halt its progression [125,126]. Further trials are now necessary to fully evaluate the effects of RAS blockade in DR before such treatment can be used clinically.

Natural anti-inflammatory therapies

Recently, more attention has been paid to natural molecules able to supplement conventional therapies for DR or slow the progression of diabetes complications. Curcumin, the major chemical component of turmeric, has beneficial effects on multiple disorders due to its antioxidant, anti-inflammatory and anti-proliferative properties, as well as its novel function as an inhibitor of histone acetyltransferases [127]. Several animal studies have shown the benefits of curcumin in limiting the pathophysiological changes in diabetes through its antioxidant activities [128–130].

Curcumin affects both the neurodegeneration and vascular alterations associated with DR through various mechanisms, including preventing cellular organelle degeneration while increasing retinal capillary basement membrane thickness, decreasing TNF-α and VEGF, and increasing levels of extracellular matrix production by boosting levels of mammalian excision repair cross-complementing enzymes 1 and 4 (ERCC1 and ERCC4, respectively) [129–131]. In experimental models, curcumin has also been shown to reduce tortuosity of the microvasculature in diabetes, and to repair and regenerate the choroidal microvasculature of such affected animals [132].

Studies in vitro have shown that curcumin has inhibitory effects on the proliferation and migration of retinal endothelial cells, an important stage of DR proliferation [133–135]. Curcumin has also been shown to inhibit the production of IL-8 and MCP-1 induced by glycated human serum albumin (HSA) dose-dependently by deactivating extracellular signal-regulated protein kinases 1/2 (ERK1/2) in human retinal pigment epithelial (RPE) cells [136].

Sesamin (the main component of sesame seeds and sesame oil) has proved to be an important antioxidant with neuroprotective properties, and a possible therapeutic option in DR. In one study of streptozotocin (STZ)-induced DR in mice, sesamin slowed the progression of diabetic retinal injury by decreasing blood glucose levels, suppressing microglia activation, reducing retinal TNF-α and ICAM-1 levels, and inhibiting iNOS expression [137].

Resveratrol, a natural antioxidant present in grapes, red wine and other berries, has beneficial effects in many ocular diseases due to its physiological effects in modulating inflammation, neovascularization and apoptosis [138]. Resveratrol is particularly effective as an antioxidant in the treatment of ischaemic conditions [139], and as a neuroprotective agent in various diseases involving neuronal injury, such as Parkinson's disease and stroke [140]. Resveratrol suppresses apoptosis induced by ischaemia and reperfusion injury in mouse retinal ganglion cells via downregulation of caspase-8 and caspase-3 expression. As increased expression of caspase-8 and caspase-3 mRNA indicate apoptosis activation, this is strongly correlated with activation of the apoptotic pathway [141].

Anthocyanins are important natural pigments responsible for the red/blue colour of fruits, leaves, seeds, stems and flowers in a variety of plant species. These health-promoting phytochemicals are potentially protective against oxidative stress in some degenerative diseases, and have anti-inflammatory, antibacterial, anticancer and cardioprotective properties. Thus, anthocyanins may also have a beneficial role in DR [142].

Palmitoylethanolamide (PEA) is an endogenous cell-protective lipid with anti-inflammatory and neuron-protective properties [143]. It is thought to protect the retina via its anti-inflammatory properties, to prevent oxidant stress, and to inhibit overactivation of Müller cells, microglia and astrocytes. PEA also inhibits overactivation of various glial cells and expression of NF-κB, thereby decreasing levels of proinflammatory molecules and cytokines, and downregulating reactive gliosis. This has been shown in both mixed neuroglial and organotypic hippocampal cultures [144]. Furthermore, PEA inhibits toll-like receptor 4 (TLR4) activity and downregulates TLR4-triggered inflammation cascades [143]. TLRs play an important role in innate immune responses, inflammation and the pathogenesis of DR [145].

Bromelain is a cysteine protease found in pineapple juice and stems, and some studies have demonstrated an efficacy similar to that of standard anti-inflammatory drugs [146], although its precise mode of action is unclear [146]. Bromelain has also been shown to enhance immune defences and to inhibit angiogenesis [147]. Due to its anti-inflammatory and anti-angiogenic activities, it may be useful in several therapeutic areas [147].

Finally, multiple studies have demonstrated the cytotoxic and antiproliferative effects of the boswellic acids in *Boswellia serrata* [148]. Indeed, it has been observed that boswellic acids and their derivatives can interfere with NF-κB signalling [149] through binding and inhibiting κB kinases and, subsequently, modulating NF-κB signalling [150]. Nevertheless, further studies need to be carried out to establish the clinical anti-inflammatory value of these molecules in DR.

Conclusion

A complex and widespread disease such as DR needs to be treated with a combination of therapies acting at different levels. Recent studies of anti-VEGF drugs have led scientists to consider them the first-choice treatment for DR and its complications, thereby replacing the laser treatment in use for some 30 years with their IV injection. However, anti-VEGF therapy is very expensive, as it requires frequent follow-ups and re-treatments (an average of 13 IV injections per patient over 3 years), and is also difficult to manage in everyday clinical practice, making it barely sustainable by national health systems. This means that many diabetes patients with DR have general health problems, yet are unwilling to come in for monthly injections and monitoring during the first 6–12 months of therapy. Moreover, chronic therapy with anti-VEGF can increase cardiovascular risk in this population of patients. Thus, it is important to find combination treatments that can reduce the number of IV injections required.

Inflammation plays a crucial role in the pathogenesis of DME: chronic inflammation causes neurovascular damage and ischaemic neovascularization, but is not significantly affected by anti-VEGF treatment. However, anti-inflammatory treatment has often allowed the number of IV anti-VEGF injections to be reduced. Also, in certain categories such as pseudophakic patients, anti-inflammatory treatment with steroids and laser had comparable results to those observed with anti-VEGF injections.

Treatment with corticosteroids, especially in the novel form of slow-release implants, is increasingly gaining in popularity, particularly for the treatment of poor and incomplete responders to anti-VEGF therapies and laser photocoagulation, and the treatment of patients with chronic, long-term DME. However, the currently available corticosteroid therapies are only partially effective and not without side effects. Thus, a wide range of new drugs has been proposed as an option for future DME treatments. Nevertheless, to clarify their role in clinical practice whether individually and in association with other types of treatment, further large-scale studies are now needed.

Disclosure of interest

The authors declare that they have no competing interest.

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