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Review Article

A Universal Ophthalmic Drug: Is it a Reality?

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Abstract

Background: Minocycline is a second-generation, semisynthetic tetracycline used over decades as a broad-spectrum antibiotic, but recently new properties were discovered beyond antibiotic activity. There are multiple biological bases for the possible protective effect of minocycline on eye structures.

The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions that minocycline may be useful in the treatment of various eye diseases.

Keywords: *Minocycline; Ocular Inflammation; Neuroprotective Effect; Antioxydative Action; Retinal Degeneration; Glaucoma; Retinal Vein Occlusion; Diabetic Retinopathy*

Introduction

Minocycline is a highly lipophilic semisynthetic second-generation tetracycline antibiotic with a broad-spectrum antibiotic activity [1], which was synthesized by Lederle Laboratories in 1967 and became widely available [2].

Taken into account that minocycline is the lipid-soluble and has the greatest permeability of all tetracyclines through the blood-brain barrier, it may, in the future, be appropriate for treatment of certain CNS disorders [3]. This is in addition to its known antimicrobial properties. Minocycline can reduce neuronal death after excitotoxicity and ionizing radiation in culture [4,5] and in animal models of stroke [5-7], Parkinson's disease [8,9], Huntington's disease [10], amyotrophic lateral sclerosis [11] and multiple sclerosis [12].

There is evidence for the neuroprotective effect of minocycline in neurodegenerative diseases [13,14]. At the same time the drug has a good antioxydative activity [15] and anti-inflammatory effects unrelated to its antimicrobial activitiy [16,17]. Pharmacokinetics of oral minocycline have shown that the drug is rapidly absorbed, with a prolonged half-life, reaching high concentrations within the eye [18,19].

The above sources appear to indicate there are multiple biological bases for the possible protective effect of monicycline on eye structures. The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions that minocycline may be useful in the treatment of various eye diseases.

Minocycline in Retinitis Pigmentosa

Retinitis pigmentosa (RP) represents a group of progressive hereditary diseases of the retina that lead to incurable blindness [20] and principally characterized by progressive rod-dominant photoreceptor degeneration in the initial stage and eventual cone photoreceptor degeneration in later stages. Advanced disease is also accompanied by changes in the macula [21,22] more commonly manifested by macular edema with currently unknown underlying mechanism.

It is supposed that an inflammation plays a role in this process. Taken into account the anti-inflammatory properties of minocycline recently in May 2014 the National Health Institute has initiated a Trial Study of Oral Minocycline in Treating Bilateral Cystoid Macular Edema Associated With Retinitis Pigmentosa, which will be completed in May 2016 [23]. We are close to the announcing of the evidence-based results. RP has been known to be initiated by photoreceptor apoptosis as a final common pathway at the cellular level, irrespective of gene mutations.

A recent study of Peng., *et al*. [24] asseccing the effect of minocycline in the experimental rd 10 mouse model of human retinitis pigmentosa evidenced that minocycline has been shown to protect photoreceptors from apoptosis due to its neuroprotective effects through both anti-inflammatory and anti-apoptotic mechanisms. Currently available long-term (140 month) findings of one patient with retinitis pigmentosa treated initially by deprenyl (1 mg/day), a safe antiapoptotic agent, and followed by minocycline (100 mg/day) at month 76 have revealed usefulness of minocycline in preventing decline of visual field [25]. Based on these case results it is not possible to rule out an additional effect from the deprenyl, or a synergistic effect of the combination.

Minocycline in Glaucoma

Glaucoma is currently recognized to be a multifactorial, progressive, neurodegenerative disorder. It is characterized by the acquired death of retina ganglion cells (RGC) and loss of their axons as well as optic nerve atrophy and loss of neurons in the lateral geniculate nucleus and the visual cortex [26]. In cytological study conducted by Bosco., *et al*. [27] minocycline has been shown to inhibit apoptosis of retinal neurocytes cultured at high pressure *in vitro*.

Few studies have focused on the neuroprotective activity of minocycline in the experimental mouse model of glaucoma [28-31]. The general consensus is that minocycline have a positive impact on preventing apoptosis. According to findings of Levkovitch-Verbin., *et al*. [28] minocycline upregulates pro-survival genes and downregulates apoptotic genes. Yang., *et al*. [31] suggested that minocycline inhibited the increased expression of the precursor form of nerve growth factor in microglia, the p75 neurotrophin receptor in astroglia, protecting cells from apoptosis. Findings by Bosco., *et al*. [29,30] obviate that minocycline reduced microglial activation. At the same time Kernt., *et al*. [32] evidenced that the drug protects optic nerve head astrocytes and trabecular meshwork cells. The general consensus is that a prevention of apoptosis after minocycline treatment, mainly due to its neuroprotective effect, suggests a potential application of minocycline in glaucoma. However, no clinical trials have been conducted yet.

Minocycline in optic nerve crush

Neuroprotective properties of minocycline were also tested in the optic nerve crush (ONC) in experimental approach using a mouse model [33]. The left eye of each adult male mice underwent ONC, followed by randomization into minocycline-treated group and saline-treated control group. The mice without receiving ONC injury were used as positive controls. Researchers have demonstrated that in the early stage after ONC (at Days 4 and 7), the density of RGCs in the minocycline-treated group was higher comparing to the saline-treated group and concluded that neuroprotective effect of minocycline is generated in the early stage after ONC in mice, partly through delaying autophagy process and regulating transcriptional factor- NF (nuclear factor) -κB2 pathway.

Minocycline in Retinal Vein Occlusion

Retinal vein occlusion (RVO) as a vasooclusive disorder of the retinal vein is the most common visually disabling disease after diabetic retinopathy, which affects 16 million persons worldwide [34], and is a frequent cause of vision loss and even blindness [35,36].

The pathogenesis of RVO is multifactorial with both local factors and systemic diseases being etiologically important. Depending on the location of the obstruction, the RVOs can be divided into central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). In CRVO the obstruction is located in the central vein, at the level of the optic nerve, so most of the retina is affected [37]. In BRVO, the obstruction is located in one of the branches of the central vein, affecting only part of the posterior pole and the portion of the peripheral retina drained by occluded branch [38].

Experimentally the use of minocycline in a rat model of branch retinal vein occlusion was evaluated by Sun., *et al*. [39] with a comprehensive work-up with fundus photography , fluorescein angiography (FA) , optical coherence tomography (OCT), full field electroretinography (ffERG) *in vivo* and the measurement by real-time PCR levels of apoptosis related genes and inflammation related genes. Microglia, the primary resident immune cell of the retina, mediate and regulate multiple inflammatory changes, and according to the results minocycline have shown to inhibit the activation of microglia and to prevent the apoptosis of retinal ganglion cell . The investigators proved that in the early stage of BRVO treatment by minocycline leads to decrease of retinal edema with a maintance of retinal function. To confirm the rationale for using minocycline in the branch retinal vein occlusion and central retinal vein occlusion the National Health Institute have initiated the Clinical Trials [3].

BRVO study is currently recruiting participants. In case of CRVO the Trial started on September 2011 should be completed on January 2016. This study is a pilot, double-masked, randomized single-center study, using 100 mg minocycline or placebo orally twice daily during 24 months in addition to standard-of-care anti-VEGF intravitreal injections. In the near future we hopefully will receive the evidence-based information on medical benefit of minocycline in retinal vein occlusion.

Minocycline in Age-Related Macular Degeneration

Age-related macular degeneration (AMD) as a progressive late onset disease affecting central vision is the leading cause of irreversible blindness among older adults, affecting one in three people aged 75 or older, and with the aging population the problem is increasing [40].

Traditionally it is recognized two types of macular degeneration: nonexudative or dry and exudative or wet. The hallmark of the nonexudative form is the deposition of extracellular material beneath the retinal pigment epithelium (RPE) that leads to the formation of drusen. Both atrophic and hypertrophic changes occur in the RPE underlying the central macula and can lead to the loss of retinal photoreceptors [41,42]. Geographic atrophy (GA), sometimes referred to as the atrophic or "dry" form of AMD is an advanced form of AMD, with the global prevalence of 0.66% in all ages, but it occurs in 1.3% of people from 75-84 years old, and 4.4% of people over 85 years old. GA affects more than 8 million people worldwide, and more than one million in the U.S. Geographic atrophy is the greatest risk factor for advancing from dry AMD to wet AMD. Regretably at present therapy for the treatment or prevention of GA does not exist. Based on aforementioned the National Eye Institute collaborated with Foamix, a clinical-stage, specialty pharmaceutical company in the development of an effective therapy for GA using Foamix's stable patented topical OilGel® formulation containing minocycline [43].

To evaluate an effectiveness of oral minocycline in the treatment of geographic atrophy associated with age-related macular degeneration it initiated a Clinical Trial in September 2015 [44] which is currently recruiting participants.

In exudative form of AMD, pathologic choroidal neovascular (CNV) membranes develop under the retina, which can leak fluid and blood, and, ultimately, cause a centrally blinding disciform scar over a relatively short time course if left untreated [42,44].

Currently AMD is characterized by chronic neuroinflammation, in which the microglial cells are trigerring the inflammatory response [45]. The overactivation of microglia causes excessive production of inflammatory mediators, which ends by toxic impact to neurons, further contributing to retinal neurodegeneration [46,48]. For the first time Wirostko., *et al*. [48] based on anti-inflammatory effects advocated oral minocycline therapy for AMD management, suggesting that it will be useful not only in the early AMD , but at the same time in advanced disease through blocking neovascularization.

The laboratory study conducted by Kernt., *et al*. [49] evaluated retinal pigment epithelium degeneration in age-related macular degeneration and have focused on the cytoprotective effects of minocycline. It was recognized that minocycline effectively saves human RPE cells from oxidative damage, but at the same time taken into account the photosensitising properties of the drug, it will be evaluated further for use in AMD treatment.

Zhao., *et al*. [50] in a mouse model of subretinal hemorrhage due to neovascular AMD evaluated the impact of minocycline as an inhibitor of microglia and evidenced that *in vitro* it retarded chemotactic cytokines and *in vivo* decreased infiltration of microglia preventing photoreceptor cell loss. Additionally, into laser-induced CNV minocycline causes a significant increase in lectin (+) cells in the subretinal space anterior to CNV and a decrease in dextran-perfused neovessels compared to controls [51].

The only open-label clinical trial assessing the safety and efficacy of the combined treatment of reduced-fluence verteporfin photodynamic therapy (PDT), intravitreal ranibizumab, intravitreal dexamethasone and oral minocycline for choroidal neovascularisation secondary to AMD in 19 patients was conducted by Sivaprasad., *et al*. [52]. It was recognized the safety and maintenance of stable vision following treatment protocol. At the same time, in that study, the authors postulated that if this pilot combination trial findings are compared to outcomes of clinical trials on combination treatment with standard dose PDT and intravitreal ranibizumab in neovascular AMD, it has beem shown that outcomes were not significantly different. The likely explanations of the results is that minocycline was used in combination with aggressive invasive procedures- intravitreal injections of ranibizumab and dexamethasone together with photodynamic therapy, and it is not possible to separate and evaluate the impact of minocycline, particularly taken into account the drugs interactions, possibly nonsynergetic.

Developing an understanding of the pathophysiological mechanisms of AMD will may in the future allow the implementation of minocycline as a novel treatment option.

Minocycline in Diabetic Retinopathy

Diabetic retinopathy (DR) is a major cause of vision loss, taken into account the growing cases of diabetes mellitus in the modern world [53,54].

Currently available findings shed a light on the pathophysiology of DR and have discovered the chronic inflammation with the generation of pro-inflammatory cytokines, causing harmfull impact on retinal vessel and neurotoxic effect on retinal cells [55-57]. At the same time, microglia is a universal mediator of multiple inflammatory changes, playing a role also in diabetic retinopathy. Various *in vitro* and *in vivo* studies have described the microglial proliferations in DR [58-63]. Zeng., *et al*. [58] compared the quantity of microglial cells of healthy persons to patients with diabetic retinopathy. The authors proved quantitative and hypertrophic changes of the microglia corresponding to different stages of the disease. The similar changes were revealed in different mouse models of DR [59-62], supporting the underlying mechanism for progression of diabetic retinopathy. Aforementioned evidenced the role of microglia as therapeutic cellular target in DR. Few studies have focused on the minocycline use to prevent activation of microglia [61-63]. The results from the study conducted by Krady., *et al*. [62] suggest that minocycline retards the inflammatory cytokine production, and decreases the release of cytotoxins from activated microglia. The general consensus is that minocycline blocks the microglial alterations in DR. Taken into account the accompanying apoptosis of neurons in the diabetic retina [62] minocycline have also proposed to prevent DR, in relation to its neuroprotective effects in retinal cells. Researchers have demonstrated that minocycline has antiapoptotic effect through decreasing caspase-3 activity within the retina. Similar benefits of minocycline on apoptosis in DR confirmed by ERG -findings was shown in the latest study conducted by Wu., *et al*. [64] assecing the impact of drug in a rat diabetic retinopathy model. Diabetes was simulated in the 34 rats , 24 from which with further randomization to two experimental groups orally receiving different doses of minocycline - 2.5 mg/kg and 5 mg/kg respectively during 8 weeks and remnant 10 served as a control group. Another 10 weight-matched healthy rats were included into normal control group.

The amplitudes of the b wave of ERG and oscillary potentials (OPs) were measured and compared in four groups - two study and two controls. The results evidenced that in the diabetic rats, retinal poly (ADP ribose) polymerase 1 (PARP 1) gene expression was markedly upregulated, the number of apoptotic cells and the activity levels of caspase 3 were increased, and the amplitude of the ERG b wave and the OPs were markedly lower as compared with the normal rats. Following treatment with minocycline, the abnormal expression of PARP 1 in the retina was inhibited, and cellular apoptosis was decreased.

Based on the fact that inflammation and specifically activation of microglia plays a role not only in DR pathogenesis, but also in diabetic macular edema (DME). Cukras., *et al*. [65] initiated and conducted the first pilot clinical trial on oral minocycline. The authors of this U.S. based single-center, prospective, nonrandomized, uncontrolled open-label phase I/II clinical trial investigated the safety and potential efficacy of oral minocycline, as an inhibitor of microglial activation, in the treatment of DME.

They enrolled 5 participants with fovea-involving DME, who received oral minocycline 100mg twice daily for 6 months. Main outcome measurements included best-corrected visual acuity (BCVA), central retinal subfield thickness (CST) and central macular volume (CMV) using spectral domain optical coherence tomography (SD-OCT) and late leakage on fluorescein angiography (FA). The authors found that the study drug was well-tolerated and not associated with significant safety issues. They reported that, in study eyes, mean BCVA improved continuously from baseline at 1, 2, 4, and 6 months by +1.0, +4.0, +4.0, and +5.8 letters, respectively, while mean retinal thickness (CST) on OCT decreased by –2.9%, –5.7%, –13.9, and –8.1% for the same time points. At Month 6, mean area of late leakage on FA decreased by –34.4% in study eyes. Mean changes in contralateral fellow eyes also demonstrated similar trends. Additionally, improvements in outcome measures were not correlated with concurrent changes in systemic factors. According to the authors, in this pilot proof-of-concept study of DME, minocycline as primary treatment was associated with improved visual function, central macular edema and vascular leakage, comparing favorably with historical controls from previous studies.

In summary, microglial inhibition and neuroprotection with oral minocycline may be a promising therapeutic strategy which targets the inflammatory etiology of DME.

Conclusion

There are multiple biological bases for the possible protective effect of Minocycline in eye diseases. The rationale for using minocycline in such retinal diseases as retinitis pigmentosa, glaucoma, retinal vein occlusion, age-related macular degeneration and diabetic retinopathy appear to involve a combination of neuroprotective, anti-inflammatory and antioxydative effects. In view of the growing evidence of possible effectiveness of minocycline pharmacotherapy we hopefully shall soon see its development as a "universal" ophthalmic drug. This therapeutic modality offers promise in the area of retinal therapeutics.

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