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Pharmacogenetics of ranibizumab on diabetic retinopathy

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ABSTRACT

Diabetes is the leading prevalent worldwide metabolic disease and a growing global problem. 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). Ranibizumab is highly effective in the treatment of DME, but some cases have failed to respond well to this drug, resulting in severe visual loss. VEGF-A polymorphisms may be the reason for the patients' poor response to ranibizumab. In the near future, gene therapy may become a part of routine clinical practice for DR. Further research in the field of pharmacogenetics and gene therapy is required to realize the full potential and limitations of this strategy.

Keywords: Pharmacogenetics, ranibizumab, VEGF, diabetic retinopathy.
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INTRODUCTION

Diabetes is the leading prevalent worldwide metabolic disease and a growing global problem. 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 main complications of DR and the preeminent cause of visual impairment in the working-age populace in the Western world.[1] Clinically, DR is divided into two stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).[2] NPDR represents the early stage of DR, wherein improved vascular permeability and capillary occlusion are two fundamental observations in the retinal vasculature. PDR is characterised by the development of new vessels and can be further defined by their location and severity. With regards to location, there may be: new vessels on the disc or within 1 disc diameter (DD) of the margin of the disc (NVD); elsewhere in the retina (NVE); on the iris (NVI); or anterior chamber angle (NVA). Classification of PDR severity includes: early PDR (NVD 1/4 DD, NVE without haemorrhage); PDR with high-risk characteristics such as NVD equal to or greater than 1/4 DD, any NVD- or NVE-associated vitreous haemorrhage; florid (aggressive presentation) PDR; and gliotic (with the development of fibrotic tissue) PDR. 'Involutionary' PDR refers to new vessels that have regressed, usually in response to treatment but (rarely) spontaneously.[3]

Treatment options for proliferative diabetic retinopathy (PDR) include panretinal photocoagulation (PRP), anti-vascular endothelial growth factor (anti-VEGF) therapy, and vitrectomy.[4] Vitrectomy is generally reserved for cases of non-clearing vitreous haemorrhage or traction retinal detachment threatening or involving the macula. Although PRP has been general care for over 40 years, 5 current medical trial outcomes suggest anti VEGF therapy is a lifelike alternative to PRP for therapy of PDR thru at least 2 years, contingent on affected person compliance and get right of entry to therapy.[4,5] In humans, the VEGF family is composed of several members: VEGF-A (which has different isoforms), VEGF-B, VEGF-C, VEGF-D, VEGF–E (viral VEGF), VEGF-F (snake venom VEGF), placenta growth factor (PlGF), and, recently, to this family has been added endocrine gland-derived vascular endothelial growth factor (EG-VEGF).[6] In accordance with findings from animal models, studies in DR sufferers have proven increased PlGF stages in the retina, vitreous, and aqueous humors. In fact, the unbalanced expression ranges of pro-angiogenic factors, such as PlGF and VEGF-A, and angiogenesis inhibitors, such as the pigment epithelium-derived component (PEDF), are being pointed out as the leading cause of neovascularization in DR patients. PEDF, which is primarily produced by way of the retinal pigment epithelium (RPE) in the retina, is a mighty antiangiogenic molecule that counteracts angiogenesis inducers. Additionally, PEDF has neuroprotective, anti-inflammatory, and anti-oxidative properties.[7]

Several studies have identified different VEGF-A SNPs associated with DR which has been concluded by Yang *et al*. Yang *et al* performed several metanalysis regarding the relationship between BEGF gene polymorphisms and susceptibility to DR, PDR, or NPDR. They reported five SNPs on VEGF gene associated in increasing risk of DR.[8] VEGF 634(405) G/C (rs201096/rs2010963) promoter polymorphism is related with an elevated transcriptional and translational things to do of VEGF gene, which might also be accountable for the improvement of DR. This find out about suggests that VEGF 634(405)G/C (rs201096/rs2010963) is

significantly associated with the increased susceptibility of DR in two populations, ordinary and Caucasian (p = 0,004. By contrast, a previous study conducted focusing on Asian community did not support the affiliation of VEGF 634 C/G polymorphism with both DR and PDR (p>0,05). Ethnicity and genetic background would possibly play a predominant role. Many factors should determine the variations in the findings about Asian and Caucasian populations, such as sample size, study design, retinopathy grading scales, and genotyping techniques. Since sunlight exposure is a acknowledged threat thing of age-related macular degeneration, the extended exposure to sunlight in Caucasian areas should be another cause for DR.[8,9]

VEGF 5092(6112)A/C (rs2146323) protects towards DR in common (p-= 0,027) and Asian (p=0,022) populations. However, substantial affiliation was observed between rs2146323 and suggests statically raised risk of DR in Caucasians (p = 0,006). Also, one of a kind genetic backgrounds, sample size, measurement bias, and different environmental factors would possibly contribute. A mixture from distinctive variables on every study have a remarkable influence on the pooled distribution of each genotype, which would possibly be an essential element over the final outcomes in all populations. In the identical way, its role in the pathogenesis of DR would need to be further explored.[8]

Regarding VEGF 936C/T (rs3025039) and VEGF 1190G/A (rs13207351), the analysis shows a significant association between these polymorphisms and increased risk of DR in basic and Asian populations. Evermore some studies noted that 936 C/T polymorphism is no longer only an critical factor deciding plasma VEGF levels, but also correlates with DR. Although we did not determine the mechanism through which rs3025039 leads to the elevated risk of DR, our outcomes propose that VEGF 936 site is a potential regulatory site for VEGF transcription, thereby contributing to VEGF production and an increased risk for DR.[8]

VEGF 9162C/T (rs3025021) reveals as a defensive contributor to DR susceptibility in all three populations. different result is determined between Asian and Mexican population. In Asian population, a statistically significant association is mentioned in the intronic SNP rs3025021 mutant alleles and DR, suggesting that rs3025021's intron region could be either enhancers or silencers to VEGF gene expression. On the contrary, it did now not show any association between rs3025021 and DR risk in Mexican population, suggesting that wonderful populations have exclusive associations even for the identical genetic polymorphism. However, further evaluation be conducted to clarify that how rs3025021 affects each VEGF function and expression.[8]

PHARMACOGENETICS OF RANIBIZUMAB

Ranibizumab is a recombinant humanized monoclonal antibody fragment that binds to all isoforms of VEGF-A. Its structure is that of a monoclonal antibody FAB (fragment antigen binding) fragment, which is derived from bevacizumab, a full-length humanized monoclonal antibody against human VEGF. At present, ranibizumab is produced by *Escherichia coli* cells with the use of recombinant DNA technology. The vascular endothelial growth factor (VEGF) pathway has a key role in regulating angiogenesis, as a consequence triggering signaling processes that promote tumor growth. Increased levels of VEGF-A are present in vitreous and aqueous fluid of patients with proliferative diabetic retinopathy, diabetic macular edema, and glaucoma. By high affinity to the VEGF-A isoforms (e.g., VEGF110, VEGF121, and VEGF165), Ranibizumab prevents binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Once VEGF-A is bound to its receptors it promotes endothelial cell proliferation and neovascularization, and leads to vascular leakage by affecting the tight junction proteins.[10,11]

A randomized clinical trial has been conducted by Gross et. Al. The authors enrolled evaluated 394 study eyes with PDR enrolled February through December 2012 thru January 2018. Eyes were randomly assigned to receive intravitreous ranibizumab (n = 191) or PRP (n = 203). Frequency of ranibizumab was based on a protocol-specified retreatment algorithm. Although loss to follow-up used to be pretty high (approximately 66% aside from deaths), visual acuity in most study eyes that completed follow-up was very correct at 5 years and was similar in each groups (adjusted difference, 0.6; 95% CI, −2.3 to 3.5; P = .68). Severe vision loss or serious PDR complications have been distinguished with PRP or ranibizumab; however, the ranibizumab group had lower rates of growing vision-impairing diabetic macular edema and less visual field loss.[11]

In Protocol S, 394 234 study eyes of 177 participants enrolled at 36 sites taking part in the ancillary study, 81 of 114 eyes (71.1%) in the ranibizumab group and 86 of 120 eyes (71.7%) in the PRP group. Longitudinal regression modelling was used to investigate the associations of ranibizumab injections, laser treatments, and time with total point score in the course of the follow-up period. Mean change in total point score related with time from baseline, after accounting for laser treatments and injections, was −34 (95% CI, −175 to 106) at 1 year, −48 (95% CI, −171 to 75) at two years, −125 (95% CI, −250 to 1) at three years, −168 (95% CI, −294 to −43) at four years, and −201 (95% CI, −327 to −74) at 5 years (P value for differences between times = .04). there is no definitive conclusions that can be drawn from these results, there are a couple of possible reasons for the progression of VF loss seen in the eyes treated solely with anti VEGF therapy in this study. One viable explanation is that development of the underlying diabetic retinopathy is affecting VF sensitivity. There is proof that diabetic retinal neurodegeneration progresses with duration of diabetes and may also precede signs of diabetic retinopathy. Deterioration of the VF in eyes of patients with diabetes in the absence of cure with laser or pharmacologic agents is evident by the mean deviation at baseline of approximately −6.5 dB for this cohort. Increasing retinal ischemia associated with PDR may cause further deterioration of VF sensitivity regardless of laser or anti-VEGF.[12]

First clinical experiences with anti-VEGF treatment using bevacizumab were based on smaller clinical trials including pretreated, chronic cases of diabetic macular edema., three VEGF inhibitors

are available for the treatment of DME including bevacizumab, ranibizumab and aflibercept. For ranibizumab and aflibercept large prospective and randomized clinical trials revealed excellent functional and morphological results which were clearly superior compared to other treatment options such as laser photocoagulation alone. The number of injections required ranges about 8 to 9 within the first year of treatment and decreases in the following years. After five years of follow-up, the median number of injections in year 4 and 5, respectively, was 0 and 0 in the ranibizumab with prompt laser group and 1 and 0 in the ranibizumab with deferred laser group, including 54% and 45% of eyes during year 4, and 62% and 52% of eyes during year 5 that received no injections in the ranibizumab with prompt laser and deferred laser groups, respectively. It is today commonly accepted that anti-VEGF treatment should be initiated as early as possible to receive the best possible functional result: It was observed in clinical trials that patients who were randomized into the placebo group at study entry and were then transferred to the verum group after the primary endpoint had been reached did experience an improvement of visual acuity. However, the gain of function in this group did not reach the same level as seen in patients having been randomized into the verum group from the beginning.[13]

However, each individual variability in drug response and in the adverse drug reactions represents an open issue in pharmacological therapy. The central tenet of pharmacogenetics is the personalization of the therapeutic method in order to attain the maximum clinical effect and the minimal adverse drug reactions. For this reason, pharmacogenetics and pharmacogenomics have raised increasing interest and, thanks to new technologies in molecular genetics and in genome sequencing, a great development in latest years. The discovery of specific SNPs in candidate genes, such as VEGF-A and CFH that are concerned in PDR, has allowed for investigation the conceivable pharmacogenetic relationship between these editions and therapeutic response.[11] Several published trials have produced level I evidence showing that ranibizumab is superior to laser photocoagulation for the treatment of DME. Ranibizumab has thus emerged as an excellent first-line therapy for DME, either as monotherapy or in combination with laser photocoagulation of the macula. For this reason we have reviewed the pharmacogenetic studies regarding ranibizumab as antiangiogenic on diabetic retinopathy.

Although ranibizumab is among the most used anti VEGF-A in diabetic retinopathy. Ranibizumab is highly effective in the treatment of DME, but some cases have failed to respond well to this drug, resulting in severe visual loss. VEGF-A polymorphisms may be the reason for the patients' poor response to ranibizumab. The human VEGF gene is located on chromosome 6p21.3, which contains a 14 kb-coding region with eight exons and seven introns. This gene is highly polymorphic, and some polymorphisms affect the levels of VEGF protein expression and its angiogenic effects. Thus, VEGF gene polymorphism is considered a risk factor in the development and progression of DR and DME. At same time, different responses to anti-VEGF drug therapies may be due to differences in VEGF protein expression that are caused by the VEGF gene polymorphism (table 1).[14]

In 2017, Tetikoglu and colleagues studies polymorphism VEGF-A gene and its association in ranibizumab treatments in patients with diabetic macular edema. They enrolled 95 patients with diabetes macular edema which was treated with intravitreal ranibizumab and 32 patients with PDR only. Each group then divided by two based on the response to the treatment. Each patients was genotyped for five single nucleotide variations (SNVs) in VEGF-A: rs2010963, rs2146323, rs10434, rs833069, and rs6921438. These SNVs has association towards severity of DR ,however, regarding its association with pharmacogenetic, there are no associations between the studied VEGF-A SNVs and patients' responses to the IVR therapy.[18]

CONCLUSION

The purpose of pharmacogenetics is to individualize the therapy selections in accordance to the patient's genetic profile and thus reduce the time and cost required to select the appropriate medication for the patient's ailment. Therapy with anti-VEGF sellers has emerge as the standard of care for the modern-day management of DME. However, ununiformed response to anti-VEGF agents and need for multiple injections are predominant barriers of this approach. Research in the field of pharmacogenomics has already led to the identification of several modifications in nucleic acids and other cellular proteins that might also be associated with increased severity of DR and suboptimal response to conventional therapy. This review has highlighted efficacy ranibizumab towards the microvascular complication of diabetes that is retinopathy and pharmacogenetics which influences it. There are limited and conflicting results in the literature

Table 1. Pharmacogenetics of Diabetic Retinopathy antiangiogenic ranibizumab therapy.

Gene	SNP	Results	Ref
VEGF-A	rs833069	significant association between the rs833069 polymorphism and the anatomic response to IVR in patients DR	15
	rs2146323	identified a significant association between this polymorphism and PDR in a Caucasian population	16
		Another study confirmed that early progression of DR in Japanese patients with type 1 DM is associated with the rs2146323 polymorphism	17
	rs833069	Has clear association with the severity of the DR	18

related to the association between VEGF polymorphisms and the severity of DR. Improvements in the development of drug design and techniques of intracellular gene delivery have resulted in initiation of numerous preclinical and early clinical studies for various ocular diseases, including DR. Gene therapy has thus far proven to be safe and feasible in animal models and in early clinical studies. In the near future, gene therapy might also become a part of movements clinical practice for DR. Further research in the field of pharmacogenetics and gene therapy is required to comprehend the full potential and limitations of this strategy.

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