Current Therapeutic Research 100 (2024) 100742

Contents lists available at ScienceDirect

Current Therapeutic Research

journal homepage: www.elsevier.com/locate/curtheres

Commentary

Immunogenicity and Potential for Intraocular Inflammation of Intravitreal Anti-VEGF Drugs

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ARTICLE INFO

Article history:
Received 17 October 2023
Accepted 6 March 2024

Key words:
Anti-VEGF
Immunogenicity
Intraocular inflammation

ABSTRACT

Background: Concerns of intraocular inflammation associated with intravitreal administration of anti-VEGF drugs have been risen and the exact mechanism is not yet elucidated.
Objective: To explore the relationship between immunogenicity and intraocular inflammation in intravitreal anti-VEGF drugs.
Methods: This review examines the immunogenicity of individual intravitreal anti-VEGF drugs and their potential link to intraocular inflammation.
Results: We suggest that the main cause of intraocular inflammation is the presence of pre-existing and treatment-induced antidrug antibodies, along with considerations related to the molecular structure, which includes the drug's format and size.
Conclusions: Researchers and clinicians involved in the advancement of new anti-VEGF drugs should take into consideration the factors related to intraocular inflammation that have been discussed.

Introduction

Intravitreal antivascular endothelial growth factor (VEGF) drugs are currently the main therapeutic options for the treatment of various retinal diseases, such as neovascular age-related macular degeneration (nAMD), diabetic macular edema, and retinal vein occlusion. Recently, the immunogenicity against biotherapeutics and the antidrug antibodies (ADAs) of intravitreal anti-VEGF drugs have been recognized as having the potential to induce adverse reactions such as intraocular inflammation (IOI).

Several factors influence the immunogenicity of intravitreal anti-VEGF drugs. Drug-specific factors include the molecular weight and structure, drug dosage, and administration regimen. Patient-specific factors include age, sex, general medical condition, immune status, and previous history of inflammation.[1] In terms of drug-related immunogenicity, we summarized the characteristics of the currently developed intravitreal anti-VEGF drugs in Table. Diverse molecular formats and pharmacokinetic features are associated with immunogenicity. Prior investigations described the approximate percentages of the pre-existing (found before treatment) and treatment-emergent (appeared after treatment) antidrug antibodies in each drug and possible rate of IOI: (1) single-chain variable fragment (scFv), brolucizumab, ~50% pre-existing ADAs, ~75% treatment-emergent ADAs, and 5% to 15% IOI[2]; (2) ankyrin repeat protein with mPEG-Mal (methoxypolyethyleneglycol-maleimidopropionate), abicipar pegol, ~1% pre-existing ADAs, 32% to 38.9% treatment-emergent ADAs, and ~15% IOI[3]; (3) Fab fragment, ranibizumab, ~5% pre-existing ADAs, ~10% treatment-emergent ADAs, and ~1% IOI[4]; (4) RNA aptamer, pegaptanib, ~1% pre-existing ADAs, ~1% treatment-emergent ADAs, and ~1% IOI[5]; (5) VEGFR1/2-Fc fusion protein, aflibercept, ~3% pre-existing ADAs, treatment-emergent ADAs, and ~1% IOI[6]; (6) mono clonal antibody (IgG), bevacizumab, ~1% pre-existing ADAs, ~1% treatment-emergent ADAs, and ~1% IOI[7]; (7) bispecific antibody (IgG), faricimab, ~2% pre-existing ADAs, ~10% treatment-emergent ADAs, and ~2% IOI.[8]

Recently, many biosimilar anti-VEGF drugs have been approved and released on the market. The immunogenicity profile of original anti-VEGF drugs and biosimilars have been also reported: for biosimilars of ranibizumab, incidences of ADAs in the clinical trials were (1) Byooviz (SB11) 3.5% vs Lucentis 4.5%,[9] (2) Cimerli (FYB201) 5.9% vs Lucentis 5.9%,[10] (3) Ximluci (XSB-001) 6.9% vs Lucentis 11.9%,[11] (4) LusenBS (CKD-701) 0.0% vs Lucentis 1.3%,[12]

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https://doi.org/10.1016/j.curtheres.2024.100742

Table
Characteristics of the currently developed intravitreal anti-VEGF drugs.

	Brolucizumab	Abicipar Pegol	Ranibizumab	Pegaptanib	Aflibercept	Bevacizumab	Faricimab
Format	Single-chain variable fragment (scFv)	Ankyrin repeat protein with mPEG-Mal	Fab fragment	RNA aptamer	VEGFR1/2-Fc fusion protein	Monoclonal antibody (IgG)	Bispecific antibody (IgG)
Molecular weight	26 kDa	14 kDa (protein) 34 kDa (+mPEG)	48 kDa	50 kDa	115 kDa	149 kDa	150 kDa
Binding target	VEGF-A	VEGF-A	VEGF-A	VEGF-A	VEGF-A, VEGF-B PlGF	VEGF-A	VEGF-A, Angiopoietin-2
K_D for $VEGF_{165}$	28.4 pM	2 pM	46 pM	200 pM	0.49 pM 38.9 pM (PlGF)	58 pM	3 nM 22 nM (Ang2)
Intravitreal half-life (human)	4–6 days	10–15 days	6–8 days	8–10 days	8–10 days	9–11 days	7.5 days
Clinical dose	6 mg	2 mg	0.5 mg	0.3 mg	2 mg	1.25 mg	6 mg
Molar concentration	4.52 mmol/L	1.17 mmol/L	0.21 mmol/L	0.12 mmol/L	0.34 mmol/L	0.16 mmol/L	0.80 mmol/L
Pre-existing ADA	~50%	~1%	~5%	~1%	~3%	~1%	~2%
Treatment-emergent ADA	~75%	32.0~38.9%	~10%	~1%	~3%	~1%	~10%
IOI incidence	5–15%	~15%	~1%	~1%	~1%	~1%	~2%
Retinal vasculitis incidence	1–2.5 %	0	0	0	0	0	0
On the market	Yes	No	Yes	No	Yes	Yes	Yes

ADA = antidrug antibody; IOI = intraocular inflammation; K_D = equilibrium dissociation constant; mPEG-Mal = methoxypolyethylenelycol-maleimidopropionate; PlGF = placental growth factor; VEGF = vascular endothelial growth factor.

(5) RaniEyes (LUBT010) 0.99% vs Lucentis 4.95%; for biosimilars of aflibercept, (1) SB15 0.9% vs Eylea 1.0%,[13] (2) MYL-1701P 2.8% vs Eylea 5.7%.[14] The data show that the incidence of ADAs are similar between the biosimilars and the original anti-VEGF drugs. An analysis conducted on a biosimilar of ranibizumab demonstrated that the immunogenicity was not related to the efficacy and safety in patients with nAMD.[9]

Discussion

Ongoing research aims to identify the immunogenicity of anti-VEGF drugs. Fully human protein therapeutics are less likely to cause immunogenicity because of the central and peripheral tolerance mechanisms. Antibody-derived molecules are less likely to provoke an immune response against the IgG backbone; however, highly diverse complementarity-determining regions of antibodies can be perceived as foreign by the immune system. For instance, compared to the whole IgG bevacizumab, the single-chain variable fragment brolucizumab, which consists of heavy and light chains linked by a peptide, has surfaces that are not commonly exposed in the full-length IgG structure.[15] Pre-existing antibodies against biotherapeutic products such as nonspecific immunoglobulins, rheumatoid factor, heterophilic antibodies, anticarbohydrate, and anti-Fab antibodies have been found in treatment-naive individuals, potentially due to exposure to non-human proteins with similar structures.[16] The ADAs against heavy chain Ig sequences in brolucizumab have been reported in about 50% of treatment-naive human participants, and the incidence of treatment-emergent ADA is about 75%. The mechanism mentioned above can explain this high incidence of ADA. Although ranibizumab lacks the Fc receptor similar to brolucizumab, we postulate that the remaining Fab fragment in ranibizumab might lower the possibility of developing ADAs after intravitreal injection.[17]

In addition, abicipar pegol, a currently withdrawn anti-VEGF drug due to its high IOI rate (~15%), is associated with approximately ~1% of pre-existing ADAs and 32.0% to 38.9% of treatment-emergent ADAs. There are similarities between brolucizumab and abicipar pegol in terms of high treatment-emergent ADAs: small molecular weight, 26 kDa vs 34 kDa, and no resemblance to the IgG antibody molecular format: scFv and ankyrin repeat protein. Furthermore, the molar concentration of brolucizumab (4.52 mmol/L) and abicipar pegol (1.17 mmol/L) is much higher compared to other anti-VEGF drugs on the market (Table). These molecular features could contribute to the higher concentration in the intraocular space after intravitreal injection, which may potentially worsen the immunogenicity of anti-VEGF drugs.[18] However, the pre-existing difference in the ADAs between brolucizumab (~50%) and abicipar pegol (~1%) suggest that single-chain brolucizumab may mimic naturally present antigens, while mPEG-Mal attached abicipar pegol does not.[7] Among the anti-VEGF agents, only brolucizumab was associated with a severe form of IOI, retinal vasculitis.[17] The fact that brolucizumab is the only drug with a high incidence of pre-existing ADAs might be related to the occurrence of retinal vasculitis.

The previous study on immune-complexed brolucizumab suggests the potential to disrupt the blood–retina barrier and trigger downstream immune responses, such as activating endothelial cells, inducing cytokine release, and promoting platelet aggregation. This cascade of events can lead to vascular occlusion.[15] These anti-VEGF immune complexes, along with ADAs, contribute to the mechanisms of intraocular inflammation. Challenges in the in vivo detection of anti-VEGF immune complexes have been explored. For instance, 6S-indocyanine green (ICG) maleimide-attached bevacizumab has been tested in a rat model to visualize the immune response to anti-VEGF drugs.[19]

Conclusions

Although there are insufficient data about the mechanism and factors associated with IOI after treatment with anti-VEGF agents, we propose that the primary factor is likely the existence of pre-existing and treatment-emergent ADA and the molecular structure, including the format and size. Therefore, researchers and companies that develop new drugs should consider this perspective. Additional data on the incidence of IOI after the administration of new intravitreal drugs may consolidate the connection between immunogenicity and IOI, as well as its origin. Furthermore, researchers should be cautious in drawing conclusions and should pursue additional investigations to explore the relationships between molecular structure and ADA.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Funding: This study was supported by a research grant from the Seoul National University Bundang Hospital (no. 14-2021-0001). The funding organization had no role in the design or conduct of this study.

Author Contribution

All authors (H.M.K. and S.J.W.) equally contributed to the literature search, figure creation, study design, data collection, data interpretation, and manuscript writing.

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