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The Clinical Safety Landscape for Ocular AAV Gene Therapies

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 02 August 2024 and was last updated on 02 August 2024.

INTRODUCTION

Review question / Objective What are the potential determinants that are associated with the occurrence of adverse events in ocular rAAV-based gene therapy?

Rationale Despite the enormous advantages of rAAV-based gene therapy for ocular diseases, there are still concerns about long-term efficacy and safety issues, including immunogenicity and adverse events (AEs) such as genotoxicity, hepatotoxicity, neurotoxicity and thrombotic microangiopathy. The challenges posed by immune responses against rAAV-based agents have drawn clinically significant attention in ocular diseases, along with the recent discovery of compartmentalized lymphatic system within the eye. Given the rising of this groundbreaking approach, we conducted a systematic review of the trends and safety landscape of ocular rAAV-based gene therapies.

Condition being studied Gene therapy using adeno-associated virus (AAV) as a vector represents a novel therapeutic modality to treat a wide variety of diseases by transferring engineered genetic material into target cells for the purpose of preventing, halting or reversing pathological processes. The engineered genetic material can be delivered as protein-coding or non-coding nucleic acids to implement gene augmentation or gene editing, respectively. It was not until the 1990s that the first-in-human use of recombinant AAV (rAAV) gene therapy was reported treating patients with lung cystic fibrosis. Given the distinctive attributes of their broad tissue tropism, non-pathogenic nature, favorable safety profile, and durable

transgene expression, AAV vectors have become the preferred delivery system in clinical trials and U.S. Food and Drug Administration (FDA) – approved applications. With the advancement of rAAV engineered for enhanced specificity and transduction efficacy, more than 300 clinical trials have been initiated in treating a number of major human diseases in the past two decades, including ophthalmological, neurological, metabolic, hematologic, muscular diseases as well as oncogenic and infectious disorders.

METHODS

Search strategy Item and Search Term on FDA DatabaseWebsite: Condition: Eye disease OR Ocular OR Age-related Macular Degeneration OR Diabetic Retinopathy OR Retinal Dystrophy OR Inherited Retinal Dystrophy OR Leber Congenital Amaurosis OR Retinitis Pigmentosa OR Choroideremia OR Achromatopsia OR Stargardt Disease OR Leber Hereditary Optic Neuropathy OR Bietti Crystalline Dystrophy OR X-linked Retinoschisis OR Usher Syndromes
Intervention: Gene OR Genetic OR AAV OR Adeno-associated OR Virus OR Vector OR ADVM-022 OR AGTC-402 OR AGTC-501 OR ATSN-101 OR ATSN-201 OR BIIB087 OR BIIB111 OR BIIB112 OR BS01 OR CPK850 OR GS010 OR GS030 OR GT005 OR HMR59 OR KH631 OR Luxturna OR NR082 OR OPGx-001 OR RGX-314 OR RGX-381 OR RST-001 OR VGR-R01 OR vMCO-010 OR vMCO-I OR SPK-7001 OR SPVN06 OR ZVS101e OR 4D-110 OR 4D-125 OR 4D-150
Study type: Interventional
Study start: Before 03/01/2024.

Participant or population Patients with ocular diseases (acquired diseases include neovascular age-related macular degeneration (nAMD), dry age-related macular degeneration (dAMD) and diabetic retinopathy (DR). As for inherited diseases, i.e., inherited retinal disease (IRD), there are currently retinitis pigmentosa (RP), Leber congenital amaurosis (LCA), choroideremia (CHM), achromatopsia (ACHM), Bietti's crystalline dystrophy (BCD), Leber hereditary optic neuropathy (LHON), X-linked retinoschisis (XLRS), and Stargardt disease (STGD)).

Intervention Interventional clinical trials aiming to treat ocular diseases with AAV-based gene therapy were selected.

Comparator Including immunosuppressant usage, key elements as AAV serotype, promoter, transgene products, and route of administration.

Study designs to be included Odds ratios (ORs) using univariate and multivariable logistic regression models were applied to evaluate the association between independent variables (key elements of the rAAV-based agents and application of immunosuppression) with the occurrence of main safety outcomes.

Eligibility criteria Data were extracted for analysis of trends in the field and possible factors related to safety, including (1) study characteristics (condition, age, sex, start date, phase, status, funder type, sponsor, geographic location, study design and enrollment), (2) Intervention (dose, study eye, drug information, route of administration, and immunosuppression regimen), and (3) details of adverse event and/or a specific safety outcome.

Information sources Studies on interventional trials of ocular rAAV-based gene therapy were retrieved from the FDA database website (ClinicalTrials.gov). In addition, the search was expanded to include (1) official trial documents, (2) publications in journal articles, (3) company press releases, and (4) corporate presentations.

Main outcome(s) The analysis identified 234 trials from the FDA database, and 116 clinical trials were manually screened for inclusion in the overall review.

Quality assessment / Risk of bias analysis Study selection was manually performed by two authors independently for the purpose of removing irrelevant studies from extensive machine searches.

Strategy of data synthesis Overall review: A descriptive summary of the key design elements (including trail phase, funder type, drug information, route of administration) of 116 clinical trials.
Safety Analysis: To optimize data reliability and relevance, subsequent analyses only included trials up to 2020 since limited data was disclosed after that. Odds ratios (ORs) using univariate and multivariable logistic regression models were applied to evaluate the association between independent variables (key elements of the rAAV-based agents and application of immunosuppression) with the occurrence of main safety outcomes.

Subgroup analysis Interventions included immunosuppressant usage, key elements as AAV serotype, promoter, transgene products, and route of administration.

Safety outcomes included occurrences of treatment-emergent serious adverse event (TESAE), drug-related serious adverse event (drug-related SAE), AE of special interest (AESI), ocular inflammation, iritis, vitritis, and iridocyclitis.
All variables included in the logistic regression analysis were dichotomized.

Sensitivity analysis The receiver operating characteristic (ROC) curves were used subsequently to illustrates the performance of models.

Language restriction There is no language restriction in our study.

Country(ies) involved China.

Other relevant information The percentage of missing data for all variables ranged from zero to 42.59%, while the majority of the missing data were concentrated in trials conducted at a late stage and were missing at random. Missing values underwent multiple imputation (MI) prior to logistic regression modeling 14. The MI was performed using 38 imputed datasets with 15 iterations via the 'logreg.boot' method using the "MICE" R package.

Keywords ocular; gene therapy; trials; safety.

Contributions of each author

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