Real-World Analysis of Medications Inducing Meibomian Gland Dysfunction: based on the FDA adverse event reporting system database

Xiang Li

KeyLX613@163.com

Eye Institute & Affiliated Xiamen Eye Center, School of Medicine, Xiamen University, Xiamen, Fujian, China.

Shi-Nan Wu

https://orcid.org/0000-0002-6992-9059

Si-Qi Zhang

Zhi-Jie Zhang

Meng-Yuan Wang

Cui-Ting Chen

Xiao-Dong Chen

Ran Li

Hui-Ying Liu

Nuo Dong

Article

Keywords: Dry Eye Syndrome, Meibomian Gland Dysfunction, FAERS Database, Adverse Drug Reactions, Real-World Study

Posted Date: April 15th, 2024

DOI: https://doi.org/10.21203/rs.3.rs-3943509/v1

Additional Declarations: There is no conflict of interest

Abstract

Objective: Dry Eye Syndrome (DES) poses a growing public health concern, significantly impacting quality of life. Among its various causes, Meibomian Gland Dysfunction (MGD) plays a pivotal role. This study focuses on investigating drug-induced MGD to enhance drug safety assessment.

Methods: We analyzed FDA Adverse Event Reporting System (FAERS) data from January 2004 to September 2023. Using statistical methods like the Ratio of Odds Ratios (ROR) and Proportional Reporting Ratio (PRR), we identified signals indicative of drug-induced MGD. We also categorized drugs associated with MGD.

Results: We examined 289 subjects reporting MGD adverse reactions, with an average age of 51.69 years and 65.44% being female. Adverse reaction reports have steadily increased, peaking in 2023, primarily in the United States and Europe. We identified 9 drugs linked to MGD adverse reactions, spanning ophthalmology, oncology, immunomodulation, dermatology, and the urogenital system.

Conclusion: Our study provides real-world data for swiftly identifying potential MGD-inducing drugs. It offers a robust strategy for exploring drug-MGD associations and informs pharmacovigilance strategies, aiding clinicians in optimizing drug treatments.

Introduction

Dry Eye syndrome (DES) is an ocular condition involving abnormalities in tear quantity, quality, or ocular surface stability, often accompanied by symptoms like dryness, stinging, and blurred vision. [1] DES is a complex disease, with potential causes including abnormal tear gland secretion, excessive evaporation, and inflammation of the ocular surface, all contributing to ocular discomfort and vision problems. [2]

DES primarily falls into two categories: evaporative DES and aqueous deficiency DES.[2] Epidemiological evidence suggests that DES is predominantly evaporative[3] and is commonly associated with Meibomian Gland Dysfunction (MGD).[4] The meibomian glands, located within the upper and lower eyelids, secrete lipids onto the ocular surface, forming the outermost layer of the tear film. These lipids spread easily, helping to stabilize the tear film and prevent evaporation. MGD is characterized as a persistent, widespread disorder, predominantly marked by obstruction at the terminal ducts and alterations in the quality or quantity of glandular secretions. Such pathological changes may result in tear film instability, precipitating symptoms of ocular discomfort, pronounced inflammatory responses, and various diseases affecting the ocular surface. [5]

With medical advancements, new drugs are continually emerging. These drugs hold immense potential in treating various diseases. However, some may have unexpected effects on ocular health, including triggering or exacerbating MGD. Currently, there is a consensus among experts that the use of topical or systemic medications, including Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)[6], diuretics[7], antidepressants/antipsychotics[8], hormones[9], and multivitamins[10], may increase the risk of drug-induced DES. However, there is no clear consensus or research on which drugs cause MGD. Therefore, identifying which drugs or drug types lead to MGD is crucial for the prevention of drug-induced MGD and DES.

According to previously published research, existing data primarily come from clinical trials and observational studies conducted before drug market approval. In the real world, there is currently a lack of studies on MGD

using large-scale real-world data, along with corresponding data outcomes. Due to the limitations of the studies above, research on adverse event reports from large-sample databases in real populations holds significant clinical relevance for guiding clinical practice. The Adverse Event Reporting System (FAERS), a publicly available database, is maintained by the United States Food and Drug Administration (FDA).[11]. Its purpose is to support the FDA's post-marketing safety surveillance of drugs and therapeutic biological products. Through data provided by the FDA's Safety Information and Adverse Event Reporting program, a range of drugs has been identified that may increase the risk of MGD.

The objective of this study is to analyze data on drug-related MGD in the FAERS and conduct database mining to assess the risk signals of these drugs in inducing MGD. Our goal is to identify potential risk levels that may increase drug-induced MGD, thereby providing further evidence for clinical drug selection to reduce adverse events associated with drug-induced MGD. Ultimately, we hope that this study will enhance drug safety, offer more treatment options for clinicians, and contribute to public health protection.

Materials and methods

Data sources

This retrospective pharmacovigilance study utilized data from the FAERS database (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html), covering the period from the first quarter of 2004 to the third quarter of 2023. FAERS is a platform for publishing drug adverse event information, using the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) to code adverse reactions. This global spontaneous reporting system collects adverse event reports and safety information about approved drugs and therapeutic biological products, voluntarily submitted by healthcare professionals, pharmaceutical companies, consumers, and others[12]. The database has been publicly accessible since 2004 and is updated quarterly, with data stored in ASCII or XML format. Each quarterly ASCII data set includes a database description and seven subfiles: Demographic Record (DEMO), Adverse Event Record (REAC), Drug Record (DRUG), Outcome Record (OUTC), Report Source Record (RPSR), Therapy Record (THER), and Indication Record (INDI)[13]. From January 2004 to September 2023, there were 20,214,432 original data entries; after excluding duplicate reports, there were 16,964,230 entries. Among these, there were 291 reports of adverse events related to MGD, with 289 subjects experiencing MGD adverse events; and 152 drugs associated with MGD adverse events. After removing duplicates from commercial brand names, 148 unique drugs were retained. The data-cleaning process is illustrated in Figure 1.Considering that the FAERS database is publicly accessible, and patient records are anonymous and de-identified, it does not involve informed consent or ethical approval.

[Figure 1]

Identification of ADRs

The deduplicated data were imported into MySQL software (v8.0; Oracle, Sweden). The main ID served as the key linking field (primary key) between different data files.[14] Cases were identified using the generic names and trade names in the drug therapy file, with the role code selected as PS (Primary Suspected cases). Adverse events in FAERS are coded using standardized PT from the MedDRA. This study employed standardized MedDRA® queries to identify PTs associated with MGD[15].

Statistical Analysis

In our study, we employed disproportionality analysis methods, including Reporting Odds Ratio (ROR)[16], Proportional Reporting Ratio (PRR)[17], Bayesian Confidence Propagation Neural Network (BCPNN)[18], and Multi-Item Gamma Poisson Shrinker (MGPS)[19], to identify potential adverse event signals. This approach aimed to validate our findings and reduce the incidence of false-positive safety signals. Detailed formulas and criteria for these four algorithms can be found in Tables 1 and 2. The criteria for signal generation in the ROR method include a > 3 and the lower limit of the 95% Confidence Interval (CI) > 1. For PRR signals, the criteria are a ≥ 3 and 95% CI > 1. For BCPNN signals, the criterion is IC > 0. For MGPS signals, the criteria are EBGM05 > 2 and a > 0. In our study, the selected positive signals needed to meet the criteria for both ROR and PRR methods, indicating a potential association between the drug and the event. Data processing and statistical analysis were executed utilizing R software (version 4.3.2) and Microsoft Excel 2021.

[Table 1]

[Table 2]

Results

Subject descriptive analysis

In this study, 289 subjects reported adverse reactions to MGD. The age distribution of the subjects was primarily 51.69±18.34 years, with females accounting for 65.44% (125 cases). Among females, the age range for reported MGD adverse reactions was mainly concentrated between 40-66 years (Figure 2A). Since the inception of data collection in the FAERS database, the proportion of drug-induced MGD events reported has been increasing annually, peaking in 2023 (Figure 2B). The countries with the highest number of reported drug-induced MGD adverse reactions include the United States, Canada, Spain, the United Kingdom, France, Italy, Brazil, Germany, and Hungary (Figures 2C and D). Regarding the outcomes of adverse reactions, 'Other Serious (Important Medical Events)' accounted for 66.10%, followed by 'Disability' at 16.52% (Figure 2E). Detailed demographic information is presented in Table 3.

[Table 3]

Disproportionality analysis

In the disproportionality analysis of 148 drugs reported for MGD, nine drugs with positive signals were identified. Among these drugs with positive signals, one (11.11%) is an ophthalmic drug, four (44.45%) are antineoplastic agents, two (22.22%) are immunomodulators, one (11.11%) is a dermatological drug, and one (11.11%) is a drug for urogenital system disorders. The specific actions of these drugs can be found in Table 4.

Ophthalmic medications

Within the category of ophthalmic drugs, the drug identified with a positive signal is ranibizumab, commercially known as Lucentis. [ROR (95% CI), 24.85 (7.85-78.67), PRR 24.85].

Dermatological medications

In the category of dermatological drugs, the drug identified with a positive signal is isotretinoin, with [ROR (95% CI), 41.08 (16.64 - 101.42), PRR 41.07].

Antineoplastic Drugs

In the category of antineoplastic drugs, drugs with positive signals include paclitaxel [ROR (95% CI), 87.16 (38.58 - 196.95), PRR 87.06]; bortezomib [ROR (95% CI), 38.34 (16.72 - 87.95), PRR 38.33]; docetaxel [ROR (95% CI), 15.51 (4.90 - 49.10), PRR 15.51]; and trastuzumab [ROR (95% CI), 13.03 (4.12 - 41.24), PRR 13.03].

Immunomodulating Drugs

In the category of immunomodulating drugs, the drugs identified with positive signals are Gilenya [ROR (95% CI), 8.43 (3.09 - 23.02), PRR 8.43] and dupilumab [ROR (95% CI), 2.77 (1.12 - 6.83), PRR 2.77].

Urogenital System Drugs

In the category of drugs for the urogenital system, the drug with a positive signal is allopurinol [ROR (95% CI), 26.26 (13.85 - 49.72), PRR 26.26]. Detailed information can be found in Figure 3 and Table 4.

[Figure 3]

[Table 4]

Discussion

This study, based on the FAERS database established in January 2004, conducted a comprehensive and systematic analysis of drug-induced MGD adverse reactions. To our knowledge, this is the first study to explore drug-induced MGD based on the FAERS database, providing validation through real-world data. There is a lack of sufficient foundational research exploring the mechanisms of drug-induced MGD. Our findings offer data support and a theoretical basis for reducing drug-induced MGD and guiding rational clinical medication use.

MGD is a common eyelid margin disease involving dysfunction of the meibomian glands (tiny oil glands located inside the eyelids). These glands primarily secrete lipids that form the outer layer of the tear film, helping to reduce tear evaporation and maintain eye lubrication and health. Dysfunction of these glands can lead to reduced or poor-quality lipid secretion, affecting tear film stability and resulting in dry eye symptoms and other ocular discomforts[20]. A cross-sectional study indicated that compared to younger individuals, older adults have a higher frequency of eyelid margin abnormalities (such as vascular patency, and keratinization)[21]. Other studies supporting this observation have shown that age-related changes in metabolic quality affect both polar and neutral lipid spectra[22, 23]. These findings seem to align with documented increases in the incidence and prevalence of dry eye disease with age [24]. In our study, the age distribution of subjects was primarily 51.69 ± 18.34 years, with women comprising 65.44% (125 cases). Research has observed that postmenopausal women have a higher prevalence of MGD compared to premenopausal women [25]. Our findings align with prior epidemiological research on MGD. Additionally, the weight distribution of subjects was mainly 73.67 ± 19.04Kg. Increasing observational clinical studies suggest that dyslipidemia (elevated cholesterol, triglycerides, or lipoprotein levels) can trigger the development of MGD [26]. A strong correlation exists between obesity and

dyslipidemia, suggesting obesity might also be a contributing factor to MGD, though conclusive evidence is still lacking.

In our current study, a variety of drugs were identified as causing drug-induced MGD. Based on the statistical indicators of the ROR method, including a > 3 and the lower limit of the 95% CI lower > 1, and PRR signals with a ≥ 3 and 95% CI lower > 1, nine drugs with positive signals were screened. Among ophthalmic drugs, ranibizumab is a significant cause of drug-induced MGD. Ranibizumab, a humanized recombinant monoclonal antibody fragment, targets vascular endothelial growth factor A (VEGF-A) and effectively inhibits choroidal neovascularization[27]. Ranibizumab was first approved by the FDA in 2006 for the treatment of neovascular age-related macular degeneration (NVAMD)[28]. The mode of action of Ranibizumab involves blocking the interaction between VEGF-A and its endothelial cell receptors, thereby hindering endothelial cell proliferation, vascular permeability, and neovascularization[29]. Notable adverse effects of ranibizumab encompass conjunctival hemorrhage, ocular discomfort, and vitreous floaters, along with both acute and chronic increases in intraocular pressure[30–32]. While the likelihood of systemic adverse reactions with ranibizumab is generally minimal, this risk escalates in older patients[33, 34]. A study based on the FAERS database indicated a strong positive signal for dry eye disease as an adverse reaction induced by ranibizumab[35], but no study has yet shown a correlation between ranibizumab and MGD, nor is its mechanism of action and development clear. Therefore, in clinical ophthalmic practice, physicians need to assess not only the therapeutic purpose of the drug but also consider its potential risk of inducing drug-induced MGD in patients, further optimizing the use of clinical ophthalmic drugs.

In the dermatological drug category, isotretinoin, primarily used for treating facial acne, has a positive signal. Typical ocular adverse reactions during long-term use of isotretinoin include changes in eyelids and corneal surface, tear gland abnormalities, refractive changes, retinal function abnormalities, and optic nerve head edema[36]. Our analysis indicates that the mechanism of drug-induced MGD by isotretinoin may involve abnormal meibomian gland secretion, gland atrophy, decreased tear break-up time (TBUT), increased tear film osmolarity, and symptoms of evaporative dry eye[37–39]. Therefore, when diagnosing and treating MGD patients, it is necessary to consider their history of recent dermatological drug use. Similarly, dermatologists should assess patients' ocular conditions and provide safe, personalized treatment plans.

Among antineoplastic drugs, four drugs have positive signals for causing MGD: paclitaxel, bortezomib, docetaxel, and trastuzumab. Paclitaxel, with the highest ROR value (87.16) among the nine drugs, poses a significantly high risk of inducing MGD. Paclitaxel is a microtubule stabilizer, a class of chemotherapeutic agents used to treat various malignancies, such as breast and lung cancer[40]. One rare side effect of this drug includes cystoid macular edema (CME), which often resolves or diminishes upon discontinuation of the drug[41]. A cross-sectional analysis indicates that cancer patients undergoing paclitaxel therapy, a type of neurotoxic chemotherapy, exhibit an increased likelihood of experiencing ocular surface discomfort linked to DES, particularly when peripheral neuropathy is present[41]. Regrettably, dedicated research into the mechanisms underlying paclitaxel-induced dry eye and MGD remains absent. Nonetheless, studies have demonstrated that paclitaxel therapy significantly diminishes epidermal nerve fibers that express the neuropeptide substance P, which correlates with neuropathic symptoms in rats[42]. Considering a substantial portion of the sensory nerve fibers that serve the ocular surface, especially the cornea, also express substance P[43], this could signify a potential connection between the neurotoxic effects of paclitaxel and ocular surface discomfort in affected patients, forming a focal point for future research endeavors. The proteasome inhibitor bortezomib is a novel

anticancer drug showing promise in treating refractory multiple myeloma; docetaxel is a standard chemotherapy agent for breast cancer; trastuzumab is a monoclonal antibody targeting the HER2 receptor, widely used in treating HER2-positive breast cancer. The mechanisms of these various cancer treatment drugs in inducing dry eye are mainly related to their target sites, which also play important roles in normal cells. The treatment process may adversely affect normal tissues, including changes in tear secretion and the structure and function of corneal epithelial cells, leading to drug-induced dry eye. However, the mechanisms underlying the development of MGD remain unclear. Clinical physicians should be aware of the potential long-term toxicity of chemotherapy on the ocular surface and the potential pathophysiological mechanisms, assessing ocular surface conditions in cancer patients and making targeted medication choices.

In the immunomodulating drug category, gilenya significantly induces drug-induced MGD. Gilenya stands as the inaugural oral treatment for relapsing-remitting multiple sclerosis. Fingolimod-associated macular Edema (FAME) is a notable adverse effect linked to Gilenya. The role of Sphingosine-1-phosphate (S1P) receptors in the regulation of vascular permeability and the fortification of endothelial barrier integrity is well-established. Gilenya can disrupt this barrier functionality as a structural analog of S1P, resulting in heightened vascular permeability[44]. This disruption may underlie the pathophysiological processes associated with FAME. To date, no researchers have studied the potential association between gilenya and drug-induced MGD. Detailed information on the potential mechanism of drug-induced MGD induced by Gilenya is still unclear, and further research in this area is warranted. Dupilumab, the first monoclonal antibody approved for treating moderate to severe atopic dermatitis (AD) and severe asthma in adults and children over six years of age with AD[45], has been reported in clinical trials and confirmed in real data to commonly cause ocular surface abnormalities, observed only in AD patients. Clinical manifestations are predominantly eyelid conjunctivitis; however, cicatricial ectropion, keratitis, eye pruritus, and dry eye syndrome have also been observed[45]. We have yet to find studies on the association between Dupilumab and MGD. We speculate that the mechanism of drug-induced MGD by Dupilumab could involve its ability to block the interleukin-4 receptor subunit, thereby inhibiting interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling. IL-4 and IL-13, secreted by CD4 + Th2 lymphocytes, drive various inflammatory processes, including the immunoglobulin class switch from IgM to IgE antibodies, leading to mast cell activation, which may cause damage to the meibomian glands[46]. Overall, there is currently a lack of research on immunomodulatory drugs causing MGD adverse reactions, and additional empirical evidence is needed to enhance our understanding. Thus, in this process, we can recognize that immune balance plays a significant role in the pathologic mechanism of MGD.

In the category of urogenital system drugs, allopurinol has been identified as a significant cause of drug-induced MGD. Allopurinol is an effective xanthine oxidase inhibitor primarily used to treat hyperuricemia and gout[47]. Studies have found that severe cutaneous adverse reactions induced by allopurinol are closely related to the HLA-B58:01 allele, with 94.57% of affected patients carrying this allele[48, 49]. HLA-B58:01 is a biomarker for allopurinol-induced scarring. There is currently no specific research on allopurinol's ocular adverse reactions. We speculate that allopurinol may cause an immune response in the eyes, leading to impaired meibomian gland function and consequently MGD. Therefore, urologists should assess patients' ocular conditions and exercise caution when treating hyperuricemia and gout.

In practical applications, pharmacovigilance serves as an effective tool for the identification and corroboration of potential ocular toxicities associated with medications. We have noted a change in the primary causative drugs of MGD in recent years, with antineoplastic drugs becoming a significant category causing MGD. Capturing these

changes will help find drugs with an original fundamental focus, and our study provides opportunities and strategies for capturing these changes.

However, this study is subject to certain unavoidable limitations. Initially, the voluntary basis of FAERS reporting and the non-peer-reviewed nature of some submissions may induce biases in our findings. Additionally, the absence of data on the total patient population using these medications precludes accurate determination of the true prevalence of drug-induced MGD. Furthermore, the detection of signals merely suggests a statistical correlation, necessitating further scrutiny to confirm a definitive causal link. Also, the potential influence of concurrent medications and/or existing health conditions on the development of MGD cannot be disregarded, which might impact the outcomes of our signal detection. Finally, comprehensive external validation is imperative for research concerning specific pharmaceuticals.

Conclusion

FAERS, with its large-scale population data, extensive geographic coverage, and public accessibility, has made this spontaneous ADR reporting database an important resource for studying drug-induced MGD. Our research provides evidence that can help quickly identify drugs that may contribute to MGD. Additionally, our work offers a robust strategy for future exploration of drug-related information related to MGD and provides a real-world window into the development of drug safety strategies for medication-related injuries. Nevertheless, it is crucial to acknowledge that our research, being a pharmacovigilance analysis utilizing FAERS, merely yields indications of possible links between medications and ADRs. Comprehensive exploration is essential to ascertain the actual nexus between these drugs and ADRs via rigorous scientific inquiry.

Abbreviations

DES: Dry eye syndrome; MGD: Meibomian Gland Dysfunction; FAERS: FDA Adverse Event Reporting System; ROR: Ratio of Odds Ratios; PRR: Proportional Reporting Ratio; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; FDA: U.S.Food and Drug Administration; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; DEMO: Demographic Record; REAC: Adverse Event Record; DRUG: Drug Record; OUTC: Outcome Record; RPSR: Report Source Record; THER: Therapy Record; INDI: Indication Record; ADR: Adverse Drug Reaction; PS: Primary Suspected cases; BCPNN: Bayesian Confidence Propagation Neural Network; MGPS: Multi-Item Gamma Poisson Shrinker; CI: Confidence Interval; VEGF-A: vascular endothelial growth factor A NVAMD: neovascular age-related macular degeneration; TBUT: Tear Break-Up Time; CME: cystoid macular edema; S1P: Sphingosine-1-phosphate; AD: atopic dermatitis; IL-4: interleukin-4; IL-13: interleukin-13; SCARs: severe cutaneous adverse reactions.

Declarations

Supportive foundations

The study described was supported by grants from the National Natural Science Foundation of China (NSFC no. 81970771 [to ND]), and Project supported by the Natural Science Foundation of Fujian Province,China(Grant. 2020D027 [to ND])

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: FAERS Publish Dashboard (https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard).

Authors' contributions

Xiang Li conceived the research idea. Xiang Li, Shi-Nan Wu, and Si-Qi Zhang conducted data cleaning and literature review. Xiang Li, Zhi-Jie Zhang, Meng-Yuan Wang, Cui-Ting Chen, Xiao-Dong Chen, Ran Li, and Hui-Ying Liu contributed to drafting and critically revising the work for intellectual content. Xiang Li, Shi-Nan Wu, and Si-Qi Zhang conducted the analysis and created the figures and tables. Nuo Dong provided a critical review of the manuscript. All authors have read and approved the manuscript.

Ethical considerations and informed consent

Considering that the FAERS database is publicly accessible, and patient records are anonymous and de-identified, it does not involve informed consent or ethical approval.

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

Not Applicable.

References

1. Craig, J.P., et al., TFOS DEWS II Definition and Classification Report. Ocul Surf, 2017. 15(3): p. 276-283.
2. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf, 2007. 5(2): p. 93-107.
3. Stapleton, F., et al., TFOS DEWS II Epidemiology Report. Ocul Surf, 2017. 15(3): p. 334-365.
4. Schaumberg, D.A., et al., The international workshop on meibomian gland dysfunction: report of the subcommittee on the epidemiology of, and associated risk factors for, MGD. Invest Ophthalmol Vis Sci, 2011. 52(4): p. 1994-2005.
5. Nichols, K.K., et al., The international workshop on meibomian gland dysfunction: executive summary. Invest Ophthalmol Vis Sci, 2011. 52(4): p. 1922-9.
6. Yang, T.M., et al., Association between non-steroidal anti-inflammatory drug use and development of age-related macular degeneration-A 10-year retrospective cohort study. J Formos Med Assoc, 2023.
7. Moss, S.E., R. Klein and B.E. Klein, Incidence of dry eye in an older population. Arch Ophthalmol, 2004. 122(3): p. 369-73.
8. Paulsen, A.J., et al., Dry eye in the beaver dam offspring study: prevalence, risk factors, and health-related quality of life. Am J Ophthalmol, 2014. 157(4): p. 799-806.

9. Schaumberg, D.A., et al., Hormone replacement therapy and dry eye syndrome. JAMA, 2001. 286(17): p. 2114-9.
10. Moss, S.E., R. Klein and B.E. Klein, Prevalence of and risk factors for dry eye syndrome. Arch Ophthalmol, 2000. 118(9): p. 1264-8.
11. Rodriguez, E.M., J.A. Staffa and D.J. Graham, The role of databases in drug postmarketing surveillance. Pharmacoepidemiol Drug Saf, 2001. 10(5): p. 407-10.
12. Fang, Z., et al., A real-world disproportionality analysis of apalutamide: data mining of the FDA adverse event reporting system. Front Pharmacol, 2023. 14: p. 1101861.
13. Shu, Y., et al., A real-world pharmacovigilance study of axitinib: data mining of the public version of FDA adverse event reporting system. Expert Opin Drug Saf, 2022. 21(4): p. 563-572.
14. BERNSTEIN, H.N. and J. GINSBERG, THE PATHOLOGY OF CHLOROQUINE RETINOPATHY. Arch Ophthalmol, 1964. 71: p. 238-45.
15. Shu, Y., et al., Gastrointestinal adverse events associated with semaglutide: A pharmacovigilance study based on FDA adverse event reporting system. Front Public Health, 2022. 10: p. 996179.
16. Mao, K., et al., Signal mining study of severe cutaneous adverse events of valaciclovir or acyclovir based on the FAERS database. Expert Rev Clin Pharmacol, 2023: p. 1-10.
17. Evans, S.J., P.C. Waller and S. Davis, Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf, 2001. 10(6): p. 483-6.
18. Bate, A., Bayesian confidence propagation neural network. Drug Saf, 2007. 30(7): p. 623-5.
19. Szarfman, A., S.G. Machado and R.T. O'Neill, Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. Drug Saf, 2002. 25(6): p. 381-92.
20. Sabeti, S., et al., Management of meibomian gland dysfunction: a review. Surv Ophthalmol, 2020. 65(2): p. 205-217.
21. Hykin, P.G. and A.J. Bron, Age-related morphological changes in lid margin and meibomian gland anatomy. Cornea, 1992. 11(4): p. 334-42.
22. Sullivan, B.D., et al., Impact of androgen deficiency on the lipid profiles in human meibomian gland secretions. Adv Exp Med Biol, 2002. 506(Pt A): p. 449-58.
23. Sullivan, B.D., et al., Influence of aging on the polar and neutral lipid profiles in human meibomian gland secretions. Arch Ophthalmol, 2006. 124(9): p. 1286-92.
24. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf, 2007. 5(2): p. 93-107.
25. Siak, J.J., et al., Prevalence and risk factors of meibomian gland dysfunction: the Singapore Malay eye study. Cornea, 2012. 31(11): p. 1223-8.
26. Osae, E.A., et al., Dyslipidemia and Meibomian Gland Dysfunction: Utility of Lipidomics and Experimental Prospects with a Diet-Induced Obesity Mouse Model. Int J Mol Sci, 2019. 20(14).
27. Shahsuvaryan, M.L., Therapeutic Potential of Ranibizumab in Corneal Neovascularization. Trends Pharmacol Sci, 2017. 38(8): p. 667-668.
28. Joachim, S.C., et al., Protective effects on the retina after ranibizumab treatment in an ischemia model. PLoS One, 2017. 12(8): p. e0182407.

29. Blick, S.K., G.M. Keating and A.J. Wagstaff, Ranibizumab. Drugs, 2007. 67(8): p. 1199-206; discussion 1207-9.
30. Bressler, S.B., et al., Repeated intravitreous ranibizumab injections for diabetic macular edema and the risk of sustained elevation of intraocular pressure or the need for ocular hypotensive treatment. JAMA Ophthalmol, 2015. 133(5): p. 589-97.
31. Wang, W. and X. Zhang, Systemic adverse events after intravitreal bevacizumab versus ranibizumab for age-related macular degeneration: a meta-analysis. PLoS One, 2014. 9(10): p. e109744.
32. Kampougeris, G., D. Spyropoulos and A. Mitropoulou, Intraocular Pressure rise after Anti-VEGF Treatment: Prevalence, Possible Mechanisms and Correlations. J Curr Glaucoma Pract, 2013. 7(1): p. 19-24.
33. Falavarjani, K.G. and Q.D. Nguyen, Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. Eye (Lond), 2013. 27(7): p. 787-94.
34. Lim, L.S., et al., Emerging evidence concerning systemic safety of anti-VEGF agents--should ophthalmologists be concerned? Am J Ophthalmol, 2011. 152(3): p. 329-331.
35. Ma, P., et al., Ocular adverse events associated with anti-VEGF therapy: A pharmacovigilance study of the FDA adverse event reporting system (FAERS). Front Pharmacol, 2022. 13: p. 1017889.
36. Moy, A., N.A. McNamara and M.C. Lin, Effects of Isotretinoin on Meibomian Glands. Optom Vis Sci, 2015. 92(9): p. 925-30.
37. Mathers, W.D., et al., Meibomian gland morphology and tear osmolarity: changes with Accutane therapy. Cornea, 1991. 10(4): p. 286-90.
38. Caffery, B.E. and J.E. Josephson, Ocular side effects of isotretinoin therapy. J Am Optom Assoc, 1988. 59(3): p. 221-4.
39. Egger, S.F., et al., Ocular side effects associated with 13-cis-retinoic acid therapy for acne vulgaris: clinical features, alterations of tearfilm and conjunctival flora. Acta Ophthalmol Scand, 1995. 73(4): p. 355-7.
40. Dwivedi, R. and S. Tiroumal, POSSIBLE EFFICACY OF TOPICAL DORZOLAMIDE IN THE TREATMENT OF PACLITAXEL-RELATED CYSTOID MACULAR EDEMA. Retin Cases Brief Rep, 2018. 12(1): p. 75-79.
41. Chiang, J., et al., A cross-sectional study of ocular surface discomfort and corneal nerve dysfunction after paclitaxel treatment for cancer. Sci Rep, 2021. 11(1): p. 1786.
42. Ko, M.H., et al., Peptidergic intraepidermal nerve fibers in the skin contribute to the neuropathic pain in paclitaxel-induced peripheral neuropathy. Neuropeptides, 2014. 48(3): p. 109-17.
43. Marco, B., et al., The Effect of Aging on Nerve Morphology and Substance P Expression in Mouse and Human Corneas. Invest Ophthalmol Vis Sci, 2018. 59(13): p. 5329-5335.
44. Jain, N. and M.T. Bhatti, Fingolimod-associated macular edema: incidence, detection, and management. Neurology, 2012. 78(9): p. 672-80.
45. Costedoat, I., et al., Multicenter prospective observational study of dupilumab-induced ocular events in atopic dermatitis patients. J Eur Acad Dermatol Venereol, 2023. 37(5): p. 1056-1063.
46. Vatrella, A., et al., Dupilumab: a novel treatment for asthma. J Asthma Allergy, 2014. 7: p. 123-30.
47. Pacher, P., A. Nivorozhkin and C. Szabo, Therapeutic effects of xanthine oxidase inhibitors: renaissance half a century after the discovery of allopurinol. Pharmacol Rev, 2006. 58(1): p. 87-114.
48. Cheng, L., et al., WGCNA-Based DNA Methylation Profiling Analysis on Allopurinol-Induced Severe Cutaneous Adverse Reactions: A DNA Methylation Signature for Predisposing Drug Hypersensitivity. J Pers Med, 2022.

12(4).
49. Li, D., et al., Severe cutaneous adverse reactions to drugs: A real-world pharmacovigilance study using the FDA Adverse Event Reporting System database. Front Pharmacol, 2023. 14: p. 1117391.

Tables

Table1. Four-grid table of signal detection

Project	Target Adverse Events	Other Adverse Events	Total
target drug	a	b	a+b
Other drugs	c	d	c+d
Total	a+c	b+d	N=a+b+c+d

Notes: A contingency table for the calculation formula of the disproportionality analysis.

Table2. Four Major Algorithms Used to Assess Potential Associations Between AIs and AEs

Algorithms	Equation	Criteria
ROR	$ROR = ad/b/c$	lower limit of 95% CI>1, a≥3
	$95\%CI = e^{\ln(ROR)\pm1.96(1/a+1/b+1/c+1/d)\text{^}0.5}$	
PRR	$PRR = a(c+d)/c/(a+b)$	PRR≥2, χ2≥4, a≥3
	$\chi2 = [(ad-bc)\text{^}2](a+b+c+d)/[(a+b)(c+d)(a+c)(b$	
	$+d)]$	
BCPNN	$IC = \log_2 a(a+b+c+d)/((a+c)(a+b))$	IC025>0
MGPS	$EBGM = a(a+b+c+d)/(a+c)/(a+b)$	EBGM05>2
	$95\%CI = e^{\ln(EBGM)\pm1.96(1/a+1/b+1/c+1/d)\text{^}0.5}$	

Abbreviation: ROR, Reporting Odds Ratio; PRR, Proportional Reporting Ratio; BCPNN, Bayesian Confidence Propagation Neural Network; MGPS, Multi-item Gamma Poisson Shrinker; EBGM, Empirical Bayesian Geometric Mean; CI, Confidence Interval; χ2, Chi-square; IC, Information Component; IC025, the lower limit of the 95% one-sided confidence interval for IC; EBGM05, the lower limit of the 95% CI for EBGM.

Table 3. Baseline Data of MGD Patients Reported in the FAERS Database.

	Variables	Value
	Age (year)	51.69±18.34
	Weight (Kg)	73.67±19.04
Gender		
	Female	125 (65.4%)
	Male	66 (34.6%)
Outcome		
	Other Serious (Important Medical Event)	156 (66.1%)
	Hospitalization -Initial or Prolonged	30 (12.7%)
	Disability	39 (16.5%)
	Death	1 (0.4%)
	Life-Threatening	6 (2.5%)
	Required Intervention to Prevent Permanent Impairment/Damage Congenital Anomaly	4(1.7%)
Country		
	United States	182 (63.0%)
	Canada	14 (4.8%)
	Spain	13 (4.5%)
	United Kingdom	12 (4.2%)
	Italy	11 (3.8%)
	Germany	10 (3.5%)
	Hungary	6 (2.1%)
	France	5 (1.7%)
	Others	36 (12.5%)

Notes：Continuous numerical variables are expressed as mean ± standard deviation,and categorical variables are presented as n (%).

Table 4. Statistical values and distribution of drug-induced MGD.

Pharmaceutical taxonomy	Drug	N	ROR	ROR(95%CI)	PRR	MGPS	BCPNN	P value
Ophthalmic Medications	Lucentis	3	24.85	24.85(7.85-78.67)	24.85	9.155	4.585	<0.001
Immunomodulatory Drugs	Gilenya	4	8.43	8.43(3.09-23.02)	8.434	3.49	3.015	<0.001
Immunomodulatory Drugs	Dupilumab	5	2.77	2.77(1.12-6.83)	2.766	1.25	1.412	0.05
Genitourinary System Disorder Medications	Allopurinol	10	26.26	26.26(13.85-49.72)	26.236	14.501	4.63	<0.001
Dermatological Medications	Isotretinoin	5	41.08	41.08(16.64-101.42)	41.072	18.176	5.275	<0.001
Antineoplastic Agents	Paclitaxel	6	87.16	87.16(38.58-196.95)	87.055	42.476	6.393	<0.001
Antineoplastic Agents	Bortezomib	6	38.34	38.34(16.72-87.95)	38.335	17.824	5.158	<0.001
Antineoplastic Agents	Docetaxel	3	15.51	15.51(4.90-49.10)	15.51	5.719	3.907	<0.001
Antineoplastic Agents	Trastuzumab	3	13.03	13.03(4.12-41.24)	13.03	4.807	3.656	<0.001

Abbreviation: ROR, reporting odds ratio; PRR, proportional reported ratio; BCPNN, Bayesian confidence propagation neural network; EBGM, empirical Bayesian geometric mean; CI, Confidence Interval.

Figures

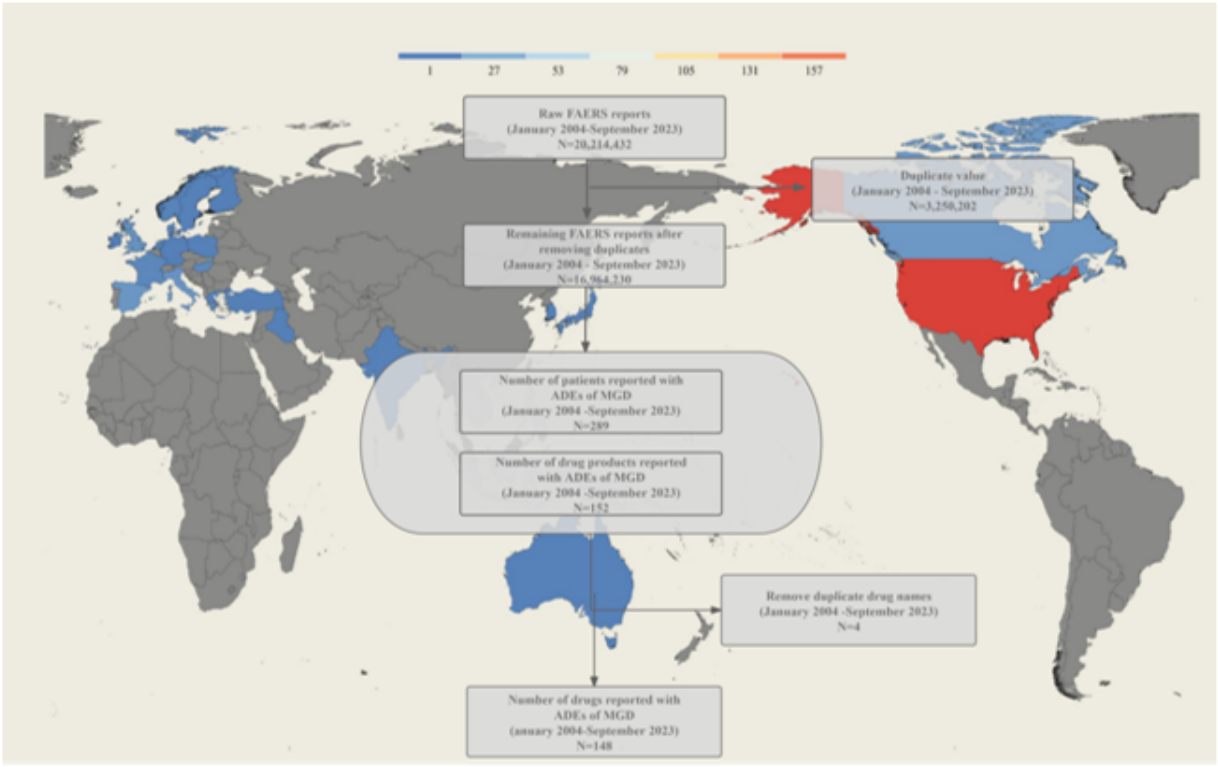

Figure 1

Flow diagram for the selection of Drug-induced MGD from the FAERS database.

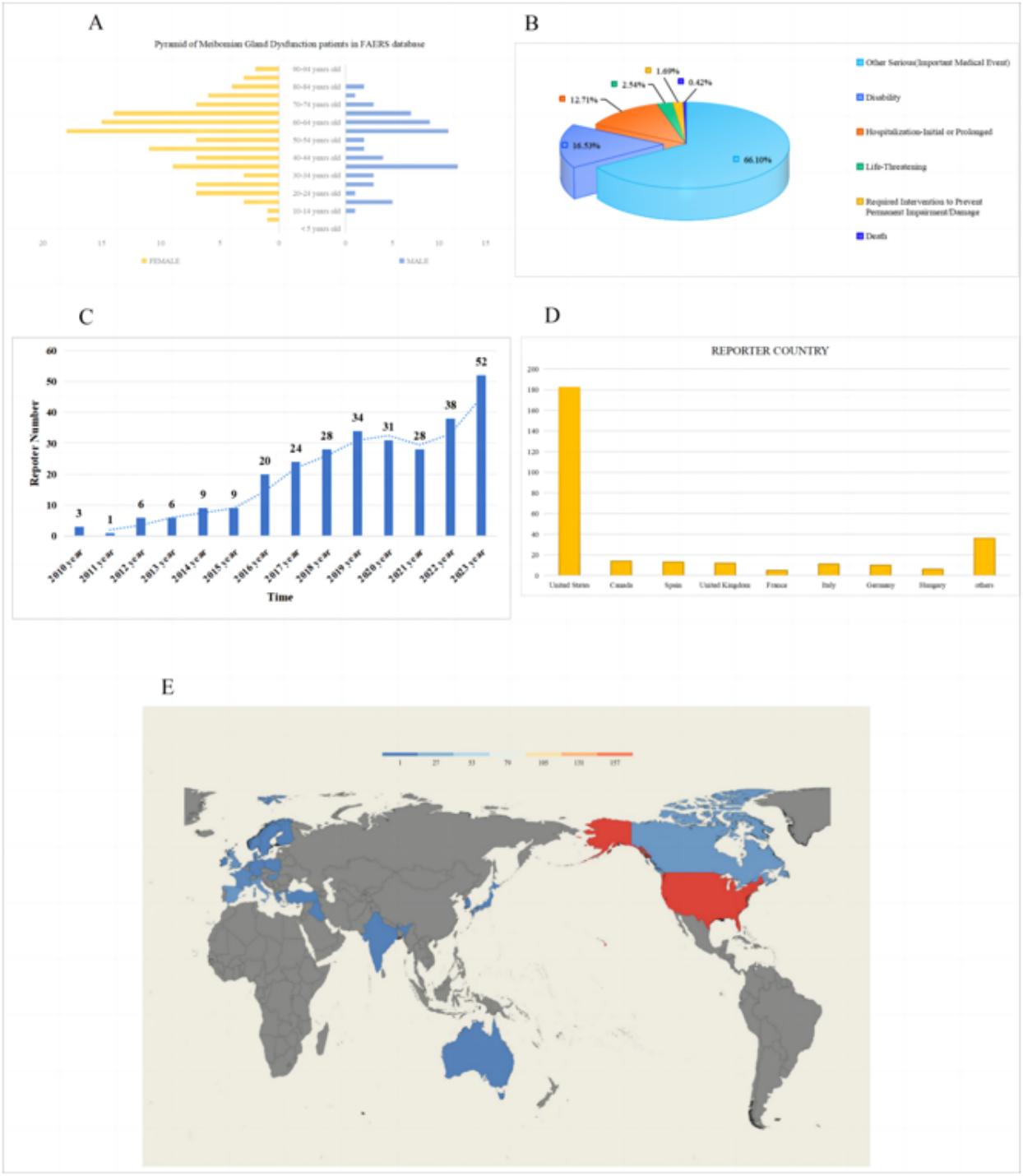

Figure 2

Distribution of Baseline Data for Patients Reporting Adverse Events of MGD in the FAERS Database.

Notes: Figure 2A depicts a pyramid chart of age distribution among patients reporting adverse events of MGD, categorized by gender.Figure 2B displays a timeline chart showing the distribution of reported adverse events of MGD over time. Figure 2C presents a histogram of the distribution of reported adverse events of MGD by country.Figure 2D showcases a heatmap of the distribution of reported adverse events of MGD by country. Figure 2E illustrates a pie chart representing the distribution of outcomes among patients experiencing adverse events of MGD.

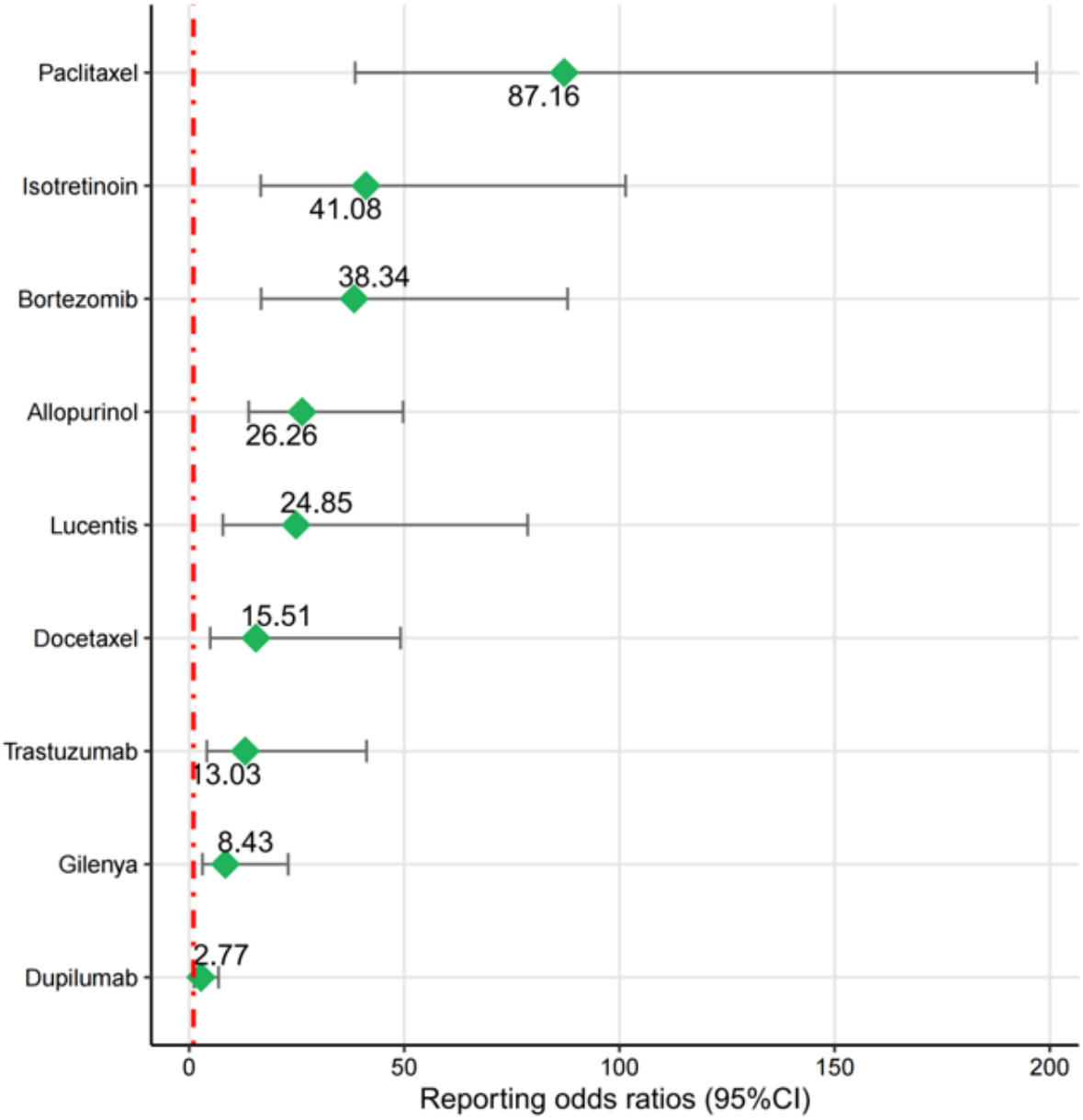

Figure 3

Forest Plot of Drugs with Positive Signals for Drug-Induced Dry Eye Based on the ROR in the FAERS Database.

Notes: Drugs associated with drug-induced MGD are predominantly distributed among ophthalmic medications, dermatological medications, immunomodulatory

medications, urological medications, antineoplastic drugs.

Abbreviation: ROR, reporting odds ratio.