BMC Ophthalmology

RESEARCH

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Risk of intraocular pressure elevation associated with triamcinolone acetonide administration via different routes in macular edema: a systematic review and network meta-analysis of randomized controlled trials

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Abstract

Purpose The local application of triamcinolone acetonide (TA) in patients with macular edema (ME) is off-label and the data are limited. We designed a systematic review and network meta-analysis to compare risk of intraocular pressure (IOP) elevation among TA for different routes of administration used by patients diagnosed with macular edema.

Methods We obtained data from the PubMed, Medline, Embase, and Cochrane Central Register of Controlled Trials for randomized controlled trials (RCTs). The outcome was IOP at 4, 12 or 24 weeks. We performed random-effects model and consistency model in the Bayesian framework with the multinma package in R. The GRADE was accorded for assess the evidence.

Results A total of 1138 citations were identified by our search, of which 16 RCTs enrolled 834 eyes (575 patients). The network showed that TA administration via different local routes and placebo were no significant differences in either pairwise or network estimates at the 4th week. IVTA (intravitreal triamcinolone acetonide) was associated with a statistically significant higher IOP at the 12th week compared to STiTA (sub-Tenon's infusion of triamcinolone acetonide) (MD: 1.67, 95% CI: 0.25 to 3.15, $P < 0.05$). IVTA, SCTA (suprachoroidal triamcinolone acetonide) and STiTA were both exhibited a statistically significant variance in IOP compared to placebo at the 24th week [(MD: 1.35, 95% CI: 0.23 to 2.30, $P < 0.05$), (MD: 2.42, 95% CI: 0.19 to 4.53, $P < 0.05$), (MD: 1.31, 95% CI: 0.02 to 2.49, $P < 0.05$)]. The probabilities of rankings and SUCRA showed that, at 4 and 12 weeks of follow-up, IVTA posed the highest risk of IOP elevation, while at the 24-week mark, SCTA exhibited the highest risk. In addition, RITA (retrobulbar injections triamcinolone acetonide) was shown to be safer.

Conclusion For the increased risk of IOP, we recommend that treatment within 4 weeks is safe. Nevertheless, it is advisable to exercise caution when administering IVTA, STiTA, SCTA beyond a duration of 12 weeks, due to the

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potential risk of IOP elevation. RITA emerged as the safest injection route in the treatment of macular edema in terms of IOP risk. However, more high-quality randomized controlled trials will be necessary to further confirm this.

Systematic review registration PROSPERO, CRD42022366513. https://www.crd.york.ac.uk/prospero/#recordDetails.

Clinical trial number Not applicable

Keywords Triamcinolone acetonide, Macular edema, Administration routes, Network meta-analysis, Bayesian framework

Introduction

Macular edema (ME) is secondary to many different ocular and systemic disease processes and is defined as the accumulation of intra and/or subretinal fluid in the macular region [1, 2]. It can occur in several retinal conditions, including diabetic retinopathy (DR), age-related macular degeneration (AMD), retinal vascular disorders, as well as various other ocular and systemic diseases, all of which can lead to visual impairment [3, 4]. At present, anti-vascular endothelial growth factor (anti-VEGF) agents, glucocorticoids, and laser photocoagulation alone or in combination are mostly used to reconstruct the blood-retinal barrier in patients with macular edema in clinical practice [5, 6]. Among these, anti-VEGF agents are currently considered the standard therapeutic regimen for ME. However, cost-effectiveness studies have raised concerns about the economic burden they impose on healthcare providers even in high-income countries [7–9]. Glucocorticoids have both angiostatic and anti-inflammatory effects, so they have been recommended by guidelines for intravitreal injection or implantation as a second-line therapy for diabetic retinal vein occlusion (RVO) and diabetic macular edema (DME), and sometimes even as a first-line treatment in special patients (e.g. high-risk cardiovascular disease, poor compliance, severe edema (>500 mm), scheduled for cataract surgery, and a history of vitrectomy) [10, 11]. Ghoraba et al. have shown that glucocorticoids as affordable low-cost alternative to anti-VEGF agents in lower-middle-income countries [12].

Glucocorticoids, such as dexamethasone and triamcinolone acetonide (TA), have long been used in the treatment of macular edema. Systemic glucocorticoids are effective but are associated with adverse events, including adrenal insuffciency, Cushing's syndrome, diabetes, cardiovascular disease, osteoporosis, and immunosuppression. Local application of glucocorticoids results in much lower systemic concentrations of the drug and reduces the incidence of adverse events associated with systemic therapy. However, these come with their own set of risks, most commonly an increased risk of cataracts and elevations in intraocular pressure (IOP) [13]. The IOP spikes may developed established glaucoma and had to rely on topical antiglaucoma treatment, and that even required glaucoma surgery due to intractable glaucoma [12]. Moreover, it's important to note that triamcinolone acetonide is not an FDA-approved medication for diabetic macular edema but is often employed off-label. There are various local routes of triamcinolone acetonide administration for treating macular edema in clinical practice. These include intravitreal triamcinolone acetonide (IVTA), sub-Tenon's infusion of triamcinolone acetonide (STiTA), retrobulbar injections of triamcinolone acetonide (RITA), suprachoroidal triamcinolone acetonide (SCTA), among others. Only SCTA released has been approved for the treatment of macular edema associated with uveitis by the FDA in 2021. Triamcinolone acetonide has been reported to be present in the eye for as long as 6 months after the injection, and it is present in measurable concentrations up to 1.5 years after intravitreal IVTA [14]. The incidence of IOP increase after IVTA may be as high as 83.3% in the literature [15]. The most recent meta-analysis indicated that sub-Tenon's capsule injection of triamcinolone acetonide injection has a comparable effect to the intravitreal injection of triamcinolone acetonide injection and carries a lower risk of intraocular complications [16].

Off-label use of triamcinolone acetonide is an unavoidable practice in the management of macular edema. Patient safety is a primary concern when it comes to off-label drug use in clinical practice. There have been many pairwise RCTs between the safety of triamcinolone acetonide in the treatment of macular edema with different routes of administration in previous. However, the safety ranking of all administration routes of triamcinolone acetonide remains unclear until now. Therefore, we conducted this systematic review and network meta-analysis (NMAs) to comprehensively evaluate and compare the safety of triamcinolone acetonide administration via different routes in patients with macular edema.

Methods

Our protocol was registered on PROSPERO (Registration No: CRD42022366513) and the study strictly adheres to the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) for Network Meta-Analyses (NMAs) (Supplementary Table 1) [17].

Search strategy and eligibility criteria

A comprehensive search was conducted across multiple databases, namely PubMed, MEDLINE (Ovid SP), Embase (Ovid SP), and Cochrane Central Register of Controlled Trials (Ovid SP), covering the period from inception to March 8th, 2023. Additionally, ClinicalTrials.gov and the reference lists of important reviews and meta-analyses were searched to augment the identified citations. The search strategy encompassed relevant terms pertaining to triamcinolone acetonide, macular edema, and randomized controlled trials. (Supplementary Table 2).

Study selection

The inclusion criteria were established utilizing the 'Patients, interventions, comparators, outcomes, study designs, timeframe' (PICOST) framework in the following manner: (1) Participants: The included patients with macular edema who were at least 18 years old; (2) Interventions and comparisons: Triamcinolone acetonide should be administered through various routes or placebo, with each treatment being administered independently and not in conjunction with any other routes of administration specified for triamcinolone acetonide in interventions.; (3) Outcomes: Intraocular pressure (IOP) change from baseline; (4) Study Design: The linguistic scope of the randomized controlled trials (RCTs), whether published or unpublished, was restricted exclusively to English or Chinese. (5) Timeframe: The duration of treatment was required to be longer than twelve weeks.

The exclusion criteria encompassed the following: (1) Animal experimentation; (2) Inclusion of participants who were pregnant or lactating women; (3) Studies published in a language other than English or Chinese; (4) Publication solely as an abstract; (5) Duplicate data publication; (6) Inability to extract data.

Screening process and data extraction

Two independent reviewers (KL and JY) utilized EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) to independently screen titles and abstracts of each eligible study, adhering to the inclusion and exclusion criteria. In cases of discrepancies, a third reviewer (NS) was consulted for resolution through discussion. The data extracted encompassed various aspects of the included studies, such as their baseline characteristics (register number/trial name, year of publication, country or countries, funding, duration), population details (disease, sample size by number of eyes, patient demographics), intervention description (route of administration, dose), and outcome measures (IOP). Regarding IOP, the mean and standard deviation values following the intervention were obtained for each study.

Quality assessment and the certainty of evidence

Two reviewers, KL and JY, independently conducted assessments of the risk of bias for all the studies included in this research, utilizing the Risk of Bias Version 2 (RoB2) tool. In cases where discrepancies arose, a third reviewer (NS) was consulted for resolution through discussion [18]. The tool is employed for assessing the potential bias in randomized trials, encompassing five distinct categories of bias: risk of bias arising from the randomization process; risk of bias due to deviations from the intended interventions; risk of bias due to missing outcome data; risk of bias in measurement of the outcome; and risk of bias in selection of the reported result. Each risk of bias evaluation dimension had three classifications: low risk of bias, some concerns, or high risk of bias.

The certainty of evidence

Two reviewers, KL and JY, conducted an independent assessment of the certainty of evidence using the GRADE approach for network meta-analysis [19–21]. Each outcome was evaluated based on various factors, including the risk of bias, incoherence, inconsistency, indirectness, intransitivity, publication bias, and imprecision. The outcomes were subsequently categorized into four levels: high, moderate, low, or very low. In case of any discrepancies, a third reviewer, NS, was consulted for resolution through discussion.

Treatment nodes

The treatment nodes were categorized based on various routes of administration for triamcinolone acetonide, and the study incorporated a dosage range of 4 to 40 mg/day for triamcinolone acetonide. The network plots were generated using the *multinma* package in R (version 4.1.3) [22].

Statistical analysis

The network meta-analysis was carried out utilizing a random-effects model and consistency model, both implemented within the Bayesian framework [23]. For the outcome variable (IOP), we employed mean differences (MDs) and 95% credible intervals (CI). The Markov chain Monte Carlo method was utilized to construct four chains, with a total of 80,000 iterations after discarding the initial 20,000 iterations as burn-in and applying a thinning factor of one. We evaluated local incoherence and derived indirect estimates through the implementation of node splitting models [24]. The surface under the cumulative ranking curve (SUCRA) was computed to establish the ranking of triamcinolone acetonide administration through various routes [25]. The *gemtc* package in R (Version 4.1.3) was utilized to perform multiple sensitivity analyses. These included: (1) the exclusion of studies with non-diabetes mellitus; (2) the exclusion of

studies with a sample size of less than 20 eyes; (3) exclusion of studies with combined laser therapy; and (4) exclusion of studies with missing populations.

Results

Characteristics of eligible studies

Figure 1 displays the flow chart of the literature search. A comprehensive review of 1138 articles and registered clinical trials was conducted, resulting in the inclusion of a total of 16 studies conducted between 2005 and 2023 in the meta-analysis. These studies met the predetermined criteria and encompassed a sample size of 834 eyes, involving 575 patients [26–41]. The main characteristics of the selected studies are collated in Table 1. Among the 16 RCTs, 1 studie was registered and 15 studies were published in English. The diseases involved were diabetic macular edema (11 RCTs), diffuse diabetic macular edema (DDME) (2 RCTs), refractory diabetic macular edema (RDME) (1 RCT), and macular edema associated with branch retinal vein occlusion (BRVO-ME) (2 RCTs). Of the included studies, 13 were two-arm studies and 3 were three-arm studies. Subsequently, we divided interventions into a placebo group and the following 4 groups: IVTA, RITA, SCTA, and STiTA. Fourteen RCTs involved IVTA compared with other routes of TA administration (the retrieved routes of administration contained RITA, SCTA, and STiTA); 6 RCTs compared triamcinolone acetonide to placebo (the retrieved routes of triamcinolone acetonide administration contained IVTA, STiTA and RITA); and 3 RCTs both the intervention group and the control group received intravitreal bevacizumab, which was a full-length humanized monoclonal antibody against vascular permeability-associated endothelial growth factor. The baseline characteristics encompassed the general composition of the study population, with men accounting for 52.01% of the participants. The age range spanned from 39.5 to 76.67 years, while the duration of follow-up varied between 12 and 24

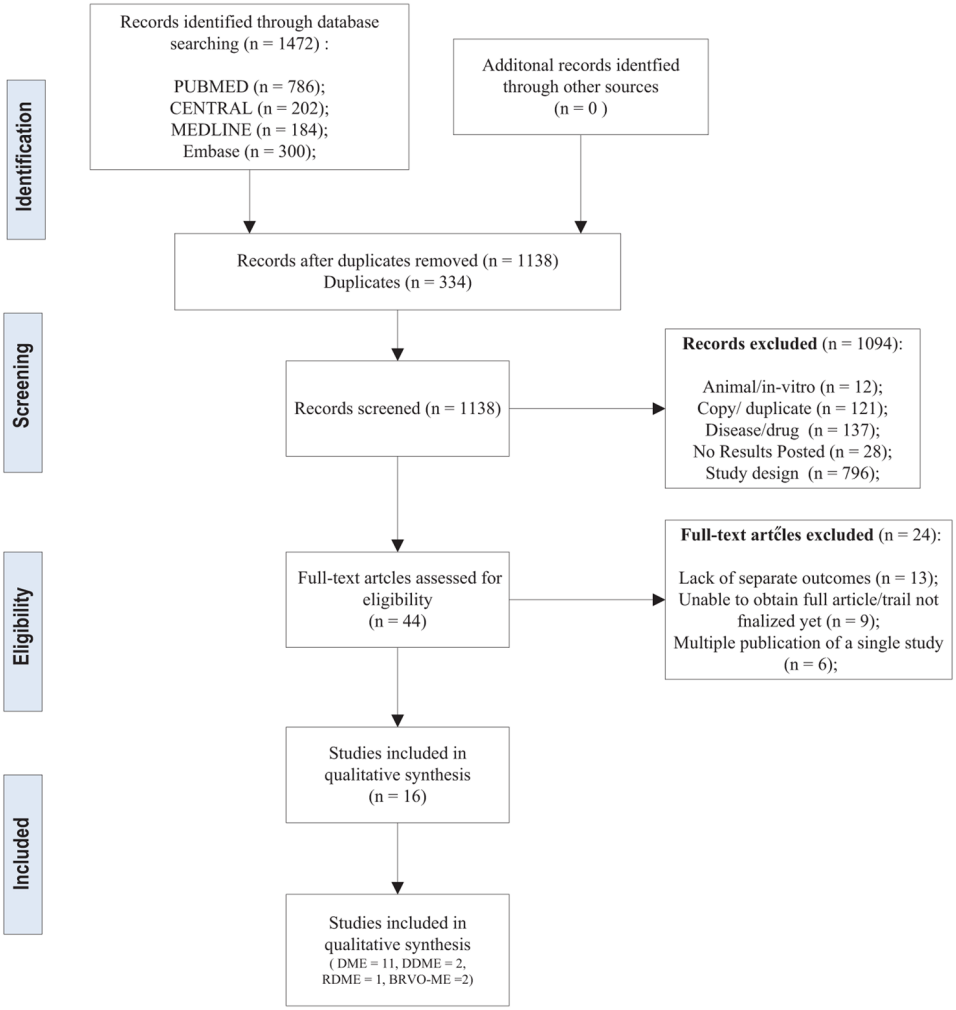

Fig. 1 Flow diagram for study identification and inclusion. Abbreviations: DME, diabetic macular edema/ oedema; DDME, diffuse diabetic macular edema; RDME, refractory diabetic macular edema; BRVO-ME, macular edema associated with branch retinal vein occlusion

Table 1 Characteristics of the studies included in the systematic review

First author	Disease	Register number/Trial name	Location	No. of eyes (*n*)	*N*	Intervention	Age (years)	Male (%)	IOP (mmHg)				Length of follow-up (weeks)
									0w	4w	12w	24w	
Abdelshafy, 2022 [26]	DME	-	Egypt	23	13	SCTA 4 mg	55 ± 3	6 (46.2%)	14 ± 2	12 ± 2	14 ± 2	-	12
					10	IVTA 4 mg	55 ± 5	3 (30.0%)	13 ± 3	15 ± 3	18 ± 4	-	
Bonini, 2005 [27]	RDME	-	Brazil	36	18	STiTA 40 mg	61.48 ± 15.19	6(42.9%)	14.57 ± 2.291	17.78 ± 2.3759	16.35 ± 2.3335	15.71 ± 1.4001	24
					18	IVTA 4 mg	62.72 ± 13.99	7(50%)	15.50 ± 2.6729	17.71 ± 1.6546	16.85 ± 1.8243	14.85 ± 2.7577	
Cardillo, 2005 [28]	DDME	-	Brazil	24	12	STiTA 40 mg	59.0 ± 9.2	5(41.67%)	14.8 ± 2.3	15.3 ± 2.6	15.8 ± 2.9	16.4 ± 3.3	24
					12	IVTA 4 mg			14.8 ± 2.1	17.8 ± 3.2	17.4 ± 3.6	17 ± 2.4	
El, 2014 [29]	DME	-	Egypt	80	40	IVTA 4 mg	55.7 ± 7.2	19(73.1%)	15.12 ± 2.37	18.17 ± 5.93	17.02 ± 4.73	15.12 ± 2.37	24
					40	STiTA 40 mg	55.8 ± 7.9	19(65.5%)	14.78 ± 2.34	16.49 ± 4.43	15.32 ± 2.56	14.96 ± 2.36	
Gillies, 2010 [30]	DME	NCT00148265	Australia	84	42	IVTA 4 mg + Laser	65.4 ± 9.5	26 (61.9%)	16.1 ± 3.0	-	19.4 ± 5.7	17.2 ± 4.2	24
					42	Laser	66.9 ± 8.9	22 (52.4%)	15.6 ± 3.4	-	16 ± 3.5	15.8 ± 3.2	
Hayashi, 2005 [31]	BRVO-ME	-	Japan	52	27	IVTA 4 mg	65.2 ± 11.3	10(37%)	14.1 ± 3.5	16.1 ± 4.3	16.6 ± 5.9	-	24
					25	RITA 40 mg	64.6 ± 10.4	10(40%)	12.9 ± 3.5	13.9 ± 3.8	13.8 ± 2.9	-	
Li, 2014 [32]	DME	-	China	64	34	RITA 20 mg + PRP	53.3 ± 13.8	38(59.38%)	13.8 ± 3.6	14.2 ± 5.3	14 ± 4.2	13.5 ± 2.9	24
					30	Placebo + PRP			14.3 ± 4.1	14.8 ± 4.9	14.6 ± 3.3	13.9 ± 3.4	
Luo, 2014 [33]	DME	-	China	40	20	STiTA 40 mg	64.7	15(75%)	18.4 ± 1.88	18.8 ± 2.77	19 ± 3.8	-	12
					20	IVTA 4 mg			18.2 ± 1.94	20.3 ± 3.69	22.6 ± 2.72	-	
Marey, 2011 [34]	DME	-	Egypt	90	30	IVTA 2 mg + IVB 1.25 mg	57.66 ± 7.44	19(63.33%)	15.67 ± 2.86	-	15.07 ± 2.05	-	12
					30	IVB 1.25 mg	57.60 ± 7.30	16(53.33%)	15.47 ± 2.93	-	15.13 ± 2.21	-	
Moon, 2016 [35]	BRVO-ME	NCT01614509	Korea	41	18	STiTA 40 mg + IVB 1.25 mg	58.83 ± 15.66	9(50.00%)	15.00 ± 2.87	-	-	15.56 ± 3.03	24
					23	IVB 1.25 mg	60.57 ± 10.68	13(56.52%)	14.78 ± 2.28	-	-	15.09 ± 2.64	
Rakhee, 2014 [36]	DDME	-	Iran	98	49	IVB 1.25 mg	54.73 ± 11.91	-	15.10 ± 1.74	-	15.45 ± 1.9	15.22 ± 1.8	24
					49	IVTA 2 mg + IVB 1.25 mg	58.18 ± 11.22		15.26 ± 1.38	-	16.83 ± 1.84	16.79 ± 1.79	
Saleh, 2017 [37]	DME	-	Egypt	34	17	IVTA 4 mg	52.53 ± 1.8	7(41.2%)	14.35 ± 2.66	17.17 ± 5.24	18.71 ± 4.51	16.88 ± 3.59	24
					17	STiTA 40 mg	56.35 ± 2.9	8(47.1%)	15.53 ± 2.9	16.29 ± 4.3	15.71 ± 4.51	16 ± 6.46	
Soliman, 2018 [38]	DME	-	Egypt	30	15	IVTA 4 mg	57.9 + 7.2	7(46.67%)	16.33 ± 1.18	19.87 ± 4.09	17.6 ± 1.45	-	12
					15	STiTA 40 mg	59.4 + 2.8	6(40%)	15.27 ± 1.58	16.2 ± 1.9	16.2 ± 1.57	-	
Takata, 2010 [39]	DME	-	Brazil	19	10	IVTA 4 mg	66.7 ± 5.1	6(60%)	14.0 ± 4.111	14.9 ± 4.111	14.9 ± 4.427	13.2 ± 2.846	24
					9	STiTA 40 mg	60.8 ± 10.4	4(44.44%)	13.8 ± 4.2	14.9 ± 5.4	14.9 ± 4.427	14.3 ± 3.9	
Wickremasinghe, 2008 [40]	DME	NCT00148330	Australia	28	13	IVTA 4 mg	61.8 ± 10.9	5(38.5%)	15.8 ± 2.8	-	17 ± 4.137	-	12
					15	Placebo	65.1 ± 11.2	7(46.7%)	16.0 ± 2.9	-	14.5 ± 3.4639	-	

Table 1 (continued)

First author	Disease	Register number/Trial name	Location	No. of eyes (n)	N	Intervention	Age (years)	Male (%)	IOP (mmHg)				Length of follow-up (weeks)
									0w	4w	12w	24w	
Zakaria, 2022 [41]	DME	NCT04069780	Egypt	43	15	IVTA 4 mg	57.67 ± 6.62	4 (33.3%)	15.20 ± 2.24	17.25 ± 3.25	16.13 ± 2.47	14.93 ± 1.54	24
					15	SCTA 4 mg	57.54 ± 6.33	2 (15.4%)	16.73 ± 2.69	18.67 ± 5.47	18.47 ± 4.53	16 ± 2.53	

Footnotes: RDME, Refractory diabetic macular edema; DDME, Diffuse diabetic macular edema; BRVO-ME, Macular edema associated with branch retinal vein occlusion; DME, Diabetic macular edema/ oedema; RLP, Retinal laser photocoagulation; MLG, Macular laser grid; PRP, panretinal photocoagulation; IVTA, Intravitreal injection triamcinolone; RITA, Retrobulbar injections triamcinolone; SCTA, Suprachoroidal triamcinolone; STITA, Sub-Tenon's infusion of triamcinolone; PLA, placebo;

Data are presented as mean ± SD, and number (percentage)

weeks. Furthermore, it is noteworthy that none of the trials received funding. pharmaceutical companies.

Risk of bias of included studies

Cochrane's Rob2 tool was used to assess the risk of bias for the 16 included RCTs. The overall risk of bias was not high. The key limitations were the lack of information on random methods and the low level of reported blinding of participants because the triamcinolone acetonide was administered by injection and could not be blinded. The assessment of the risk of bias in the included studies is shown in Fig. 2. Of the 16 studies, for selection bias, 4 studies (25%) were at low risk of bias in the randomisation process, 4 studies (25%) were at low risk of bias in deviations from the intended interventions, and 16 trials (100%) were at low risk in missing outcome data. The outcome indicator (IOP) in this analysis was objective and was not influenced by evaluators, so the 16 studies (100%) were at low risk for measurement of the outcome and selection of the reported result. Overall, three studies (19%) had a low risk of bias, thirteen studies (81%) had some concerns of bias, and no trials had a high risk of bias. A quantitative synthesis of the evidence through a network meta-analysis was deemed appropriate given the comparability in study design, outcome measures, patients involved, and inclusion and exclusion criteria. Homogeneity and consistency assumptions were confirmed.

Results of network meta-analysis

The network plots of each outcome are displayed in Fig. 3(a, b and c), showcasing the findings and quality of evidence regarding IOP at the 4th, 12th, and 24th week of triamcinolone acetonide treatment via various administration routes. The examination of heterogeneity and inconsistency in the network meta-analysis is also conducted, as depicted in Supplementary Figs. 1–6. Comprehensive details regarding the evidence for all comparisons and outcomes in the network meta-analysis can be found in Supplementary Tables 3–5. Additionally, the results of the sensitivity analysis are provided in Supplementary Tables 9–20.

IOP at the 4th week

Eleven RCTs including 432 eyes reported IOP after 4 weeks of triamcinolone acetonide administration via different routes on macular edema. The intervention nodes included in this network meta-analysis were IVTA, STiTA, RITA, SCTA and placebo. There were no significant differences in either pairwise or network estimates (Fig. 4a). The certainty of evidence was low for all comparisons except IVTA VS RITA was moderate (Fig. 4a). Detailed data are shown in the appendix (Supplementary Fig. 1 and Supplementary Table 3).

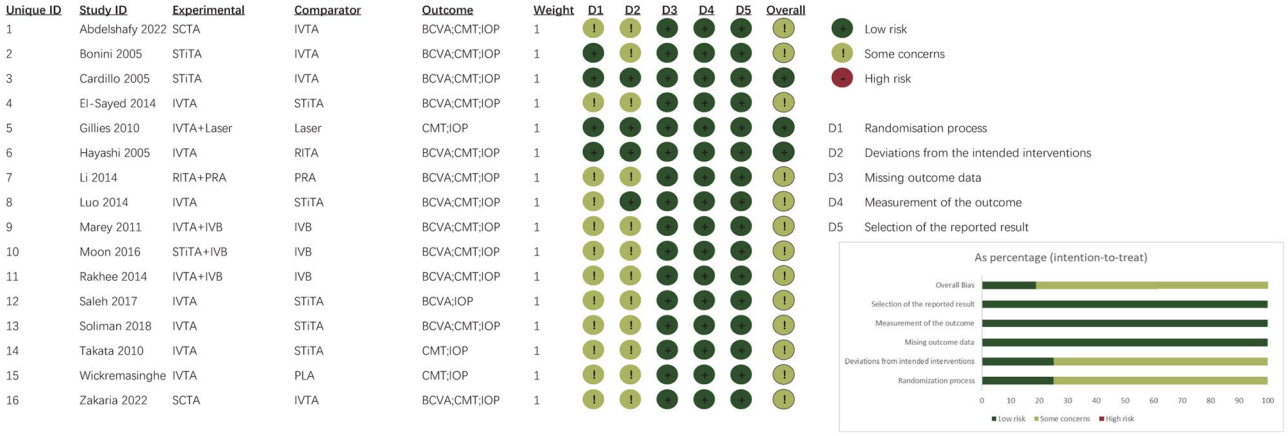

Fig. 2 Summary of the risk of bias. Footnotes: D1: Risk of bias arising from the randomization process; D2: Risk of bias due to deviations from the intended interventions; D3: Risk of bias due to missing outcome data; D4: Risk of bias in measurement of the outcome; D5: Risk of bias in selection of the reported result; Overall: Overall risk of bias

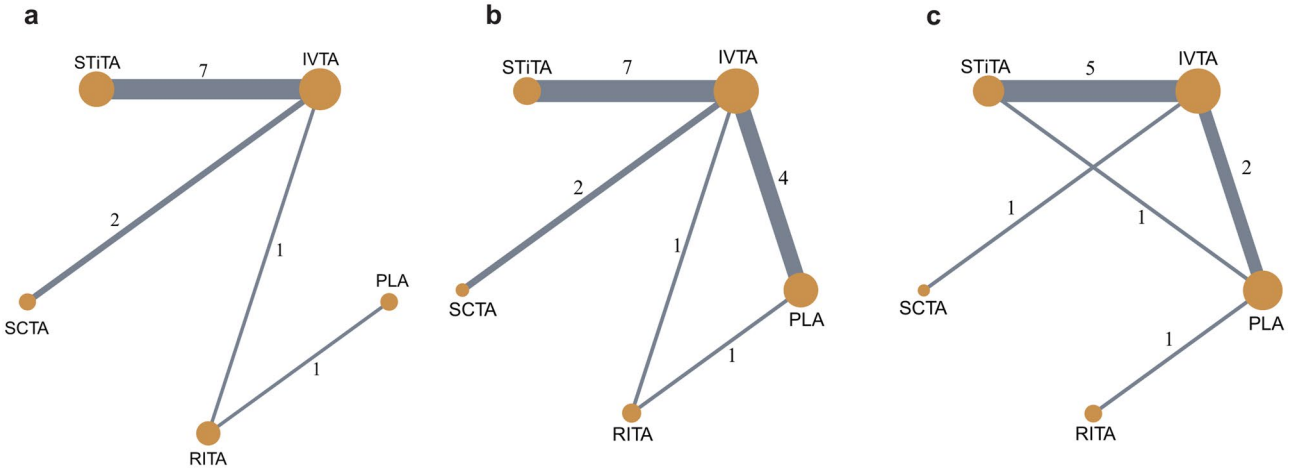

Fig. 3 Network plots of available direct comparisons. Footnotes: IOP at the 4th (**a**), 12th (**b**), and 24th (**c**) weeks. Each node (solid circle) stands for a different administration route of triamcinolone acetonide. The size of the nodes is proportional to the number of participants (i.e., sample size) involving the specific treatment intervention. The solid lines link treatments with direct comparison with the thickness proportional to the number of trials

IOP at the 12th week

Fifteen RCTs including 700 eyes reported IOP after 12 weeks of triamcinolone acetonide administration via different routes on macular edema. The intervention nodes included in this network meta-analysis were IVTA, STiTA, RITA, SCTA and placebo. Compared to STiTA, IVTA was associated with a statistically significant IOP increase at the 12th week (MD: 1.67, 95% CI: 0.25 to 3.15, $P < 0.05$], Fig. 4b), which was moderate-quality evidence. The global I^2 of pairwise was 23.8%. There were no significant differences in other pairwise comparisons, and the certainty of evidence was low for other comparisons except IVTA/RITA was moderate (Fig. 4b). Detailed data are shown in the appendix (Supplementary Figs. 2, 4, and Supplementary Table 4).

IOP at the 24th week

Ten RCTs including 507 eyes reported IOP after 24 weeks of triamcinolone acetonide administration via different routes on macular edema. The intervention nodes included in this network meta-analysis were IVTA, STiTA, RITA, SCTA and placebo. Compared to placebo, IVTA was associated with a statistically significant IOP increase at the 24th week (MD: 1.35, 95% CI: 0.23 to 2.30, $P < 0.05$], Fig. 4c), which was moderate evidence. The global I^2 of pairwise was 0%. Compared to placebo, both SCTA and STiTA were associated with a statistically significant IOP increases at the 24th week (MD: 2.42, 95% CI: 0.19 to 4.53, $P < 0.05$], MD: 1.31, 95% CI: 0.02 to 2.49, $P < 0.05$], Fig. 4c), which were moderate evidence. There were no significant differences in other pairwise comparisons, and the certainty of evidence was low for other

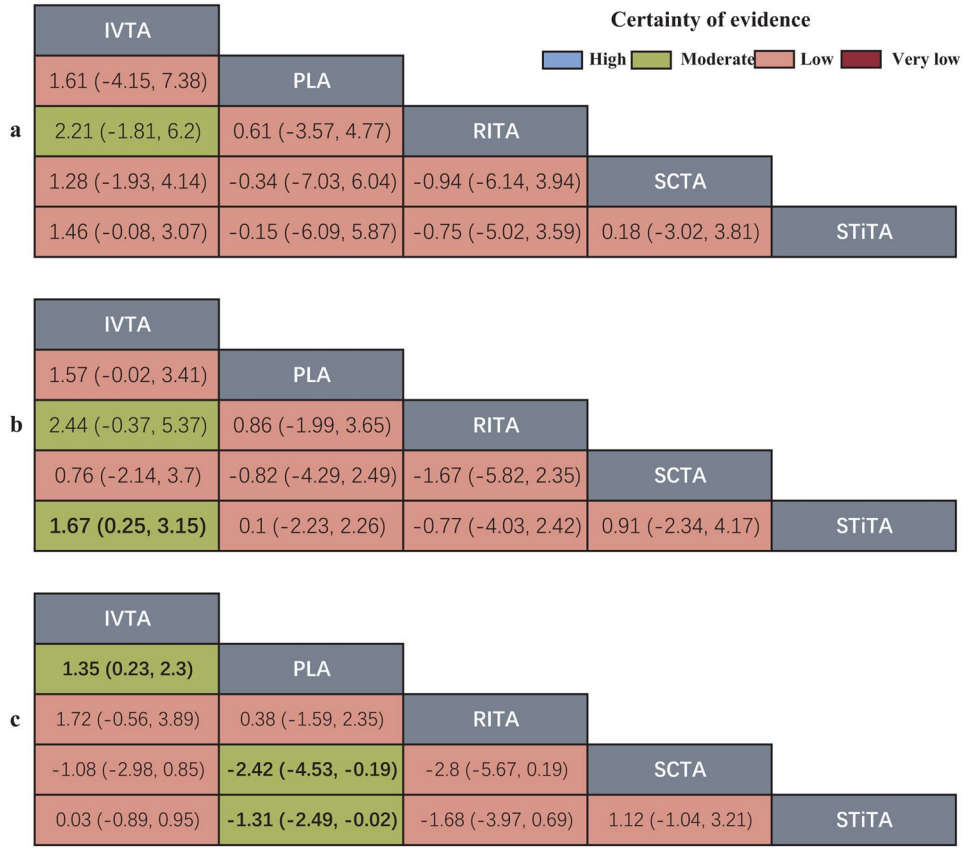

Fig. 4 League tables of outcome analyses. Footnotes: IOP at the 4th (**a**), 12th (**b**), and 24th (**c**) weeks. Bold indicates statistical significance. The color of each cell indicates the certainty of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation

comparisons. Detailed data are shown in the appendix (Supplementary Figs. 3, 5, and Supplementary Table 5).

Rankings and SUCRA

The rank probabilities of different routes of triamcinolone acetonide administration and placebo are shown in Fig. 5. The rank diagrams show that the probabilities of RITA being the safest routes of administration at the 4th, 12th, and 24th weeks was 35.50%, 57.80%, and 65.60%, respectively. The rank diagrams show that the probabilities of IVTA being among the top safety routes of administration at the 4th, 12th, and 24th weeks was always 0.00%. The SUCRA detailed data are shown in Supplementary Tables 6–8. The higher SUCRA values indicated the lower risk of IOP elevation. The highest SUCRA value of IOP at the 4th, 12th, and 24th weeks invariably was RITA (SUCRA value = 0.7041, 0.8029 and 0.8726). The lowest SUCRA value of IOP was IVTA at the 4th and 12th weeks (SUCRA value = 0.1513, and 0.1513), but changed to SCTA at the 24th week (SUCRA value = 0.0783).

Sensitivity analyses

The supplementary Tables 9–20 displays the sensitivity analyses, which align with the findings of the primary analysis.

Discussion

Treatment choice should not be solely based on treatment effectiveness but should also consider adverse event management and long-term tolerability. In particular, this treatment involves off-label use. To our knowledge, this study represents the first assess the safety of the off-label use about triamcinolone acetonide various administration routes in patients with macular edema. This systematic review and network meta-analysis involving 16 studies that enrolled 834 eyes (575 patients) provided moderate certainty evidence, which investigated the safety of triamcinolone acetonide by different routes of administration and placebo treatment for macular edema. Intraocular pressure was selected as an outcome index for safety evaluation. This paper had comparative data from randomized trials with objective outcome measures that were essential to understand which routes of injection with triamcinolone acetonide offer the optimal balance of efficacy and safety in the management of

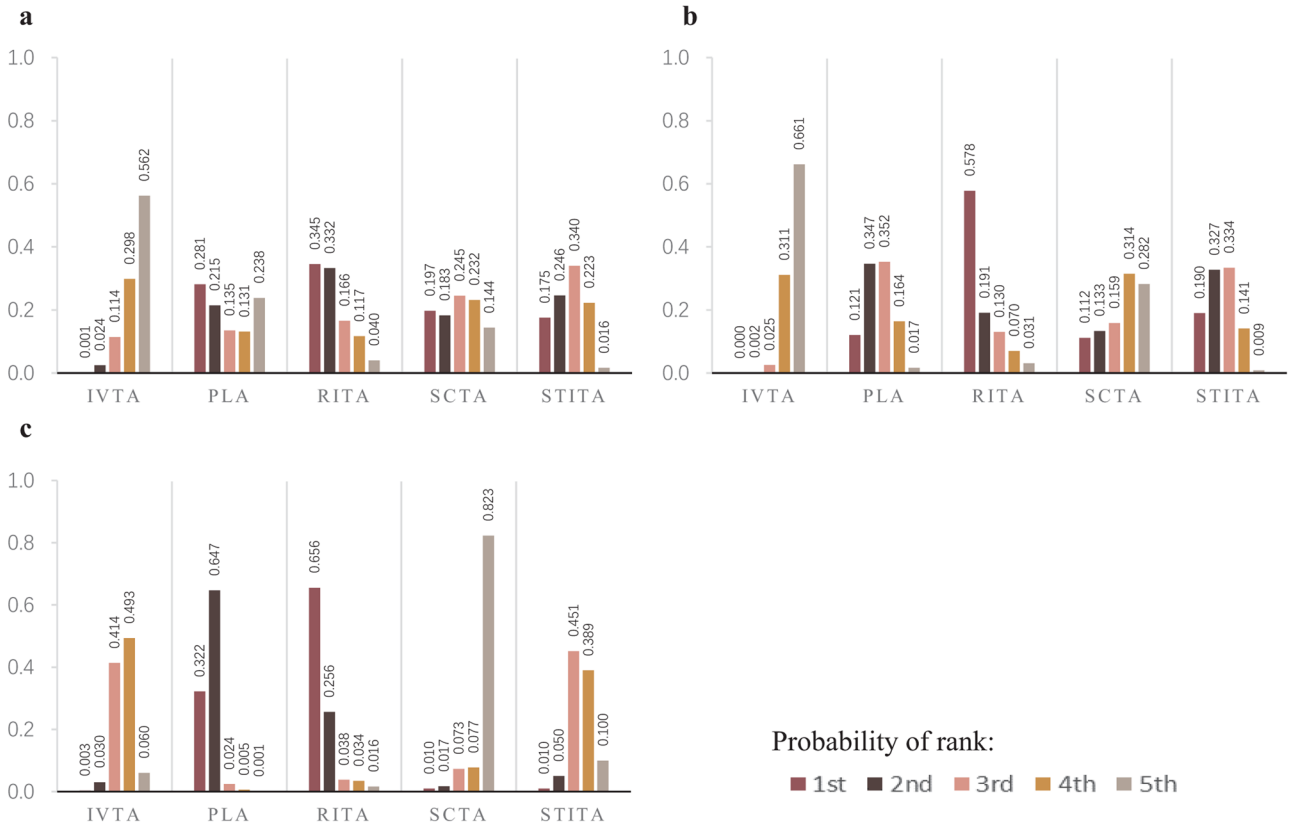

Fig. 5 Rank diagrams of outcome analyses. Footnotes: IOP at the 4th (**a**), 12th (**b**), and 24th (**c**) weeks. The numbers on the vertical axis represent the probability

these patients. The network meta-analysis found that, in early treatment (in 4 weeks), there was no significant difference in the risk of IOP between triamcinolone acetonide by different routes of administration and placebo. However, the occurrence of elevated intraocular pressure begins to manifest after 12 weeks of treatment, with a higher prevalence observed at 24 weeks. Our study revealed that the risk of IOP elevation significantly increased with the prolonged administration of IVTA, SCTA and STiTA. These risks exhibited notable differences when compared to the placebo group. According to the ranking and SUCRA values, RITA ranked highest for IOP levels from 4 to 24 weeks, while IVTA exhibited the lowest efficacy at 4 and 12 weeks. SCTA displayed lower efficacy at 24 weeks. Overall, our findings suggest that RITA may be a safer treatment option when prolonged administered.

Despite several attempts to establish its route of administration, only IVTA has been used as a second-line therapy for DME and RVO by guidelines [10, 11, 42]. However, triamcinolone acetonide is not an approved medication for DME. It has been used off-label. According to the statistical results, IVTA may be associated with a have the higher risk of IOP from 4 to 36 weeks of follow-up. This effect seems to persist even in comparison with placebo or other routes of administration. For instance, a randomized controlled trial showed that the IOP change from baseline was significantly higher in the IVT group than in the STiTA group after injection [37]. Two RCTs found that the addition of IVTA + IVB significantly increased the risk of IOP at the end of the study period compared with IVB [34, 36]. From a head-to-head trial, IVTA increased the risk of IOP compared with placebo [30]. Our results are in accordance with previous reports. which are consistent with the comparison of the network meta-analysis. Of note, a meta-analysis of IOP percentage increases from baseline levels indicated that there exists an increase in the IOP measure at its peak 4 weeks after the injection. However, 24 weeks after the injection, the increase in IOP compared to its preoperative level showed a decrease [43]. In summary, our study shows that IOP elevation is a significant side effect of IVTA injection. Careful follow-up of IOP is required after IVTA injections.

Currently, only triamcinolone suspension, released by the FDA in 2021, has been approved for the treatment of macular edema associated with uveitis as a suprachoroidal injection. However, there have been limited studies related to SCTA administration, and our inclusion criteria led to the inclusion of only 2 RCTs [26, 41]. They only

reported that regarding IOP elevation both IVTA and SCTA have insignificantly different effects. These data are consistent with those reported by the HULK study and the TYBEE study following CLS-TA injection [44–45]. All of these studies prove that triamcinolone acetonide injection has a similar effect on IOP either injected intravitreally or in the suprachoroidal space. It is noteworthy that, our network meta-analysis results shed light on the IOP effects of SCTA compared with the placebo group. SCTA had statistically a significant effect on IOP (MD, 2.42 [95% CI, 4.53, 0.19] at the 24th week. Interestingly, as indicated by the SUCRA ranking scheme, SCTA ranked last at the 24th week, replacing IVTA, which consistently ranked last at the 4th and 12th weeks.

As suggested by the SUCRA ranking scheme, RITA was consistently ranked first from 4 to 24 weeks, and STiTA was ranked behind RITA. Nonetheless, it is important to note that our network meta-analysis only included two clinical trials using RITA. Thus, the clinical significance may still be limited and unclear. Such as, Anna CK et al. have discussed in the literature concerning RITA for the treatment of thyroid eye disease-associated ophthalmopathy conditions that this procedure carries risk of sight-threatening hemorrhage [46]. While the bleeding observed following injection in their study may be attributed to the patient's prior aspirin use, no complications were directly linked to the medication itself. Although the RCTs we reviewed did not report any instances of bleeding associated with RITA, we recommend that the potential risk of post-RITA retrobulbar hemorrhage be thoroughly evaluated. hence, further research is mandatory in this context. Maggio et al. found that RITA was proposed, which had the advantage of being associated with fewer side effects when compared with IVTA, including a reduced risk of steroid-induced cataract and IOP rise, and no risk of endophthalmitis and rhegmatogenous retinal detachment [47]. This agreed with our study, we can conclude that RITA/STiTA appear to be valid alternatives to IVTA/SCTA in terms of safety outcome with a lower risk of IOP elevation. In this paper, the safety of RITA has been verified, the balanced use of RITA combined with the therapeutic effect is still required. Grzybowski et al. recommend a stepwise therapy: retrobulbar or sub-Tenon's corticosteroids in moderate pseudophakic cystoid macular edema (PCME) and intravitreal corticosteroids in recalcitrant PCME [48]. Moreover, the IOP increases after any routes of triamcinolone acetonide application are not rare, although the temporary interruption of treatment is generally not required [49]. Considering this, careful follow-up of IOP is required after each local route of triamcinolone acetonide treatment for macular edema. In conclusion, our study suggests that RITA appear to be viable alternatives to IVTA and SCTA in terms of safety, with a lower risk of IOP elevation. However, further research is needed to establish their clinical significance fully. Regardless of the route of triamcinolone acetonide treatment, careful IOP monitoring is essential.

While there is a substantial body of literature addressing the safety of IVTA, SCTA, RITA, STiTA in the treatment of macular edema, no network meta-analysis has compared these commonly used therapies. The strengths of our review include the most comprehensive synthesis of evidence to date on the safety of triamcinolone acetonide administered via different routes for macular edema, encompassing all recent publications. To the best of our knowledge, this is the first network meta-analysis to compare the efficacy of triamcinolone acetonide using different administration routes for macular edema. We conducted a comparative analysis of the risk of IOP at 4 weeks, 12 weeks, and 24 weeks. Our findings indicate a significant increase in the incidence of IOP in patients receiving IVTA and SCTA treatment as the duration of therapy extended. These results underscore the importance of closely monitoring IOP levels during the treatment period extending beyond 12 weeks, as well as the prompt adjustment of medication routes, if deemed necessary, to mitigate the likelihood of IOP occurrence. In addition, this study has a higher standard, due to accurate experimental types of randomized trials, identifying interventions outside of laser interference, unity of follow-up time. We used state-of-the-art approaches to categorize and present the findings using GRADE frameworks.

Limitations of our study include the limited quality of evidence, which may be caused by the limited number of RCTs. The scarcity of RCTs could potentially be attributed to safety apprehensions associated with the off-label use. It had further influence on indirect comparisons of some network estimates. The resolution of this issue could be achieved through the incorporation of high-quality RCTs. Second, the test results of triamcinolone acetonide by different routes of injection therapy showed that statistical heterogeneity was limited in randomized controlled trials, which provides limited confidence in the findings. The third limitation of this study pertains to the relatively lax inclusion criteria employed for disease classification. We included macular edema from various diseases, such as diabetes and branch retinal vein occlusion, in our network meta-analysis. the insufficient number of included literature sources prevented us from conducting a subgroup analysis on the risk of IOP based on the underlying causes of macular edema. The fourth limitation is the small sample size of some RCTs included in the present study. However, sensitivity analyses demonstrated no important differences in outcomes for all interventions.

Conclusion

In this systematic review and network meta-analysis, which included studies of patients with macular edema and at least 12 weeks of follow-up, our findings emphasize that the use of triamcinolone acetonide via different injection routes increases the risk of elevated IOP when compared to placebo. Despite the off-label use of triamcinolone, for the increased risk of IOP, we recommend that treatment within 4 weeks is safe. However, it is advisable to exercise caution when administering IVTA, STiTA, SCTA beyond a duration of 12 weeks, due to the potential risk of IOP elevation. RITA emerged as the safest injection route in the treatment of macular edema in terms of IOP risk. At 4 and 12 weeks of follow-up, IVTA posed the highest risk of IOP elevation, while at the 24-week mark, SCTA exhibited the highest risk. These conclusions may help doctors evaluate the balance of pros and cons of various routes of injection and adjust their treatment accordingly. In the future, large-scale trials are necessary to validate the risks identified in this meta-analysis.

Abbreviations

ME	Macular edema
TA	Triamcinolone acetonide
anti-VEGF	anti-Vascular Endothelial Growth Factor
IVTA	Intravitreal Triamcinolone Acetonide
OFTA	Orbital floor triamcinolone acetonide
STiTA	Sub-Tenon's infusion of triamcinolone acetonide
RITA	Retrobulbar injections triamcinolone acetonide
SCTA	Suprachoroidal triamcinolone acetonide
PLA	Placebo
NMAs	Network Meta-Analysis
RCTs	Randomized Controlled Trials
IOP	Intraocular Pressure
DR	Diabetic Retinopathy
AMD	Age-related Macular Degeneration
RVO	Retinal Vein Occlusion
DME	Diabetic macular edema
DDME	Diffuse diabetic macular edema
RDME	Refractory diabetic macular edema
PCME	Pseudophakic Cystoid Macular Edema
BRVO-ME	Macular edema associated with branch retinal vein occlusion

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12886-025-03979-z.

Supplementary Material 1

Acknowledgements

Not applicable.

Author contributions

KL and JY were in charge of study design, data collection and interpretation, the quality assessment of evidence, and manuscript preparation. KL wrote the paper. NS critically reviewed the manuscript and provided revisions. KL, JX, and LZ were involved in the statistical analysis. NS was involved in data collection, data interpretation, and the quality assessment of evidence. All authors contributed to the article and approved the submitted version.

Funding

KL was supported by grants from Sichuan Province Science and Technology Support Program (grant number 2023JDKP0059). NS was supported by grants from Sichuan Province Science and Technology Support Program (grant number 2023JDR0243) and Health Commission Program (grant number 2020 – 111). This research was supported by National Key Clinical Specialties Construction Program.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 15 December 2023 / Accepted: 13 March 2025
Published online: 25 March 2025

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