# Adjuvant Therapy With Anti-VEGF for DME, RVO & nAMD: A Systematic Review


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## Introduction

- **Anti-VEGF** revolutionised DME, RVO & nAMD –> 85% **dry macula** at 12 months[1]
- Yet **7-9 injections/eye/year** → travel burden, lost productivity, clinic load[2]
- Real-world registries: **≥ 20% lose ≥ 10 letters by 24 months** → undertreatment[3]
- 10-40 % of eyes show persistent OCT fluid despite monthly dosing[4]
- **Rationale for aqueous-suppressants** (topical CAIs ± β-blockers)
  - ↓ aqueous humour turnover → ↑ intravitreal dwell-time of biologics[5]
  - Cheap, widely available, minimal systemic risk[6]
- **Emerging adjunct options**: NSAIDs, sub-threshold micropulse laser (SML), nutraceuticals [7, 8]
- Prior small RCTs/RCS: mixed BCVA results; several show faster CMT/CRT regression or modest injection-sparing[9]
- **Aim of review** – summarise clinical impact of anti-VEGF + aqueous-suppressant vs monotherapy on:
  - Retinal thickness (µm) & fluid resolution
  - Best-corrected visual acuity (BCVA, logMAR/letters)
  - Injection frequency / interval extension

## Methods

- **Databases Searched:** MEDLINE, Cochrane Central, Web of Science, and Embase.
- **Primary Outcomes:** ΔCMT/CRT/CST/CFT, ΔBCVA, injections (#/12 mo), fluid-free interval, IOP change
- **Synthesis:** Narrative + disease-specific summary tables (no pooled meta because heterogeneity)

| | |
|---|---|
| **Inclusion Criteria** | • Adult (≥18 y) patients with DME, RVO (CRVO/BRVO/HRVO), or nAMD<br>• Comparative studies of anti-VEGF monotherapy vs anti-VEGF + adjunct (CAIs/β-blockers, NSAIDs, SML, nutraceuticals…)<br>• Reports ≥ 1 key outcome: BCVA change, OCT thickness (CMT/CST/CFT/CRT), or injection burden (frequency/duration)<br>• Minimum follow-up ≥1 month in RCTs or prospective/retrospective comparative cohorts |
| **Exclusion Criteria** | • Non–human or pediatric studies; non–English publications<br>• Case reports/series (<5 eyes), reviews, meta-analyses, or abstracts without full text<br>• Combined anti-VEGF with other surgical procedures (e.g. vitrectomy, conventional laser)<br>• Follow-up <1 month or missing all prespecified functional/anatomical outcomes |

## Results

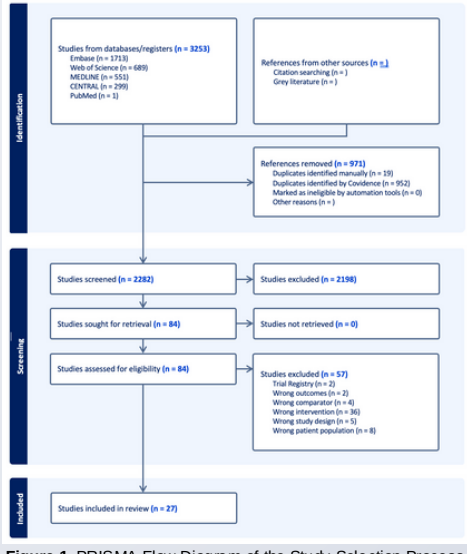


**Figure 1.** PRISMA Flow Diagram of the Study Selection Process

**Figure 2. Summary of Clinical Studies of Adjunctive Therapies with Intravitreal Anti-VEGF**

This table collates 27 comparative clinical studies of adjunctive treatments added to intravitreal anti-VEGF injections, organized by underlying retinal disease and framed by bold borders around each adjuvant class.

| STUDY ID (YR) | DESIGN / N (EYES) | ANTI-VEGF | ADJUNCT (DRUG; DOSE / FREQ / DUR) | FOLLOW-UP | ΔTHICKNESS (µM) ADJU. VS MONO | ΔBCVA (LOGMAR) | MEAN INJECTION # |
|---|---|---|---|---|---|---|---|
| **DIABETIC MACULAR EDEMA** | | | | | | | |
| FAZEL 20 | Contral-RCT / 32 | Bevacizumab ×3 | Dorzolamide 2 % BID ×3 m | 3 m | CMT: −32 µm vs −43 µm | 0.018 vs 0.032 | 3 vs 3 |
| FEKRI 24 | RCT / 46 | Bevacizumab ×3 | Timolol 0.5 % + Dorzolamide 2 % BID ×3 m | 3 m | CMT: −71 µm vs −26 µm | −0.100 vs −0.050 | 3 vs 3 |
| MIRSHAHI 19 | Contral-Pros / 22 | Bevacizumab ×3 | Timolol + Dorzolamide BID ×3 m | 3 m | CMT: −156 µm vs −84 µm | −0.330 vs −0.210 | 3 vs 3 |
| SADR 24 | Contral-RCT / 50 | Bevacizumab ×3 | Dorzolamide 2 % TID ×3 m | 3 m | CMT: −89 µm vs −38 µm | −0.051 vs −0.042 | 3 vs 3 |
| EMARA 24 | RCT / 40 | Ranibizumab ×3 | Bromfenac 0.09 % BID ×6 m | 6 m | CMT: −159 µm vs −93 µm | −0.020 vs 0.040 | 3 vs 3 |
| GABR 23 | RCT / 70 | Ranibizumab (T & E) | Bromfenac 0.09 % BID ×6 m | 6 m | CMT: −68 µm vs −29 µm | −0.107 vs −0.046 | 3.06 vs 3.26 |
| GHANBARI 17 | RCT / 80 | Bevacizumab ×1 | IV diclofenac 300 µg (single) | 4 w | CMT: −265 µm vs −219 µm | −0.228 vs −0.088 | 1 vs 1 |
| NIKKHAH 21 | RCT / 50 | Bevacizumab (PRN) | Ketorolac 0.5 % TID ×6 m | 6 m | CST: −158 µm vs −65 µm | −0.171 vs −0.149 | 4.4 vs 4.4 |
| CHATZIRALLI 22 | Prospective / 45 | Ranibizumab / Aflibercept | Nutraceutical + Resvega® PO ×12 m | 12 m | CRT: −71 µm vs −43 µm | −0.150 vs −0.120 | 6.45 vs 7.39 |
| **NEOVASCULAR AMD** | | | | | | | |
| HSU 20 | Placebo-RCT / 50 | Ranibizumab / Aflibercept | Dorzolamide 2 % + Timolol 0.5 % BID ×3 m | 3 m | CST: −37 µm vs +2 µm | +0.031 vs +0.018 | 3 vs 3 |
| LEE 19 | Retro / 15 | Bevacizumab / Aflibercept (fixed) | Dorzolamide - Timolol BID (~17 w) | ≈4 m | CST: −85 µm (single-arm) | −0.610 | – |
| SRIDHAR 16 | Single-arm / 10 | Aflibercept / Ranibizumab (fixed) | Dorzolamide - Timolol BID (~10 w) | ≈3 m | CST: −93 µm (single-arm) | −0.540 | – |
| RAHIMY 19 | CATT 2-y sec. | Ranibizumab /Bevacizumab (PRN) | Mixed β-blk/CAI (chronic, grp B) | 24 m | RT: −78 µm vs −58 µm | +0.083 vs +0.063 | 13.9 vs 15.7 |
| GOMI 12 | DB-RCT / 38 | Ranibizumab (PRN) | Bromfenac 0.1 % BID ×6 m | 6 m | CFT: −144 µm vs −94 µm | −0.19 vs −0.120 | 2.2 vs 3.2 |
| ZWEIFEL 09 | Retro / 22 | Ranibizumab /Bevacizumab | Bromfenac 0.09 % BID ×2 m | 2 m | CRT: −12 µm (no ctrl) | −0.030 | – |
| HUSUM 24 | DB-RCT / 40 | Bevacizumab (+switch T & E) | Zoledronic acid 5 mg IV q6 m | 12 m | CRT: −112 µm vs −124 µm | −0.130 vs −0.410 | 12.2 vs 11.0 |
| MANTEL 16 | Prospective / 21 | Monthly Ranibizumab / Aflibercept | Spironolactone PO 25+50 mg ×3 m | 6 m | CRT: −30 µm (no ctrl) | −0.110 | 3 vs 3 |
| DATSERIS 25 | Retro / 50 | Aflibercept (PRN) | Resvega® PO ×24 m | 24 m | CFT: −63 µm vs −64 µm | −0.160 vs −0.160 | 7.40 vs 9.32 |
| MINKOWSKI 18 | Retro / 13 | Aflibercept / Ranibizumab | Dorzolamide - Timolol (chronic) ×6 m | 6 m | CST: −70 µm (no ctrl) | – | 3.8 |
| LUO 19 | RCT / 75 | Ranibizumab (PRN) | HBOD herbal decoction PO ×6 m | 6 m | CMT: −48 µm vs −12 µm | −0.100 vs 0.000 | – |
| KAPOOR 17 | Retro / 23 | Mixed anti-VEGF | Eplerenone PO (≥3 m | ≥3 m | CMT: −65 µm (single-arm) | – | – |
| **RVO-RELATED MACULAR EDEMA** | | | | | | | |
| OBEID 21 | Prospective / 8 | Aflibercept / Ranibizumab /Bevacizumab | Dorzolamide - Timolol BID (~12 w) | ≈3 m | CFT: −79 µm (no ctrl) | −0.120 | 15.3 |
| BYEON 08 | RCT / 38 | Bevacizumab ×1 | Dorzolamide - Timolol BID (9 w) | 9 w | CRT: −349 µm vs −262 µm | −0.250 vs −0.250 | 1 |
| KARIMI 23 | RCT / 54 | Bevacizumab ×3 | Acetazolamide 250 mg BID (3 m) | 3 m | CMT: −182 µm vs −218 µm | −0.33 vs −0.39 | 3 vs 3 |
| SAISHIN 17 | DB-RCT / 45 | Ranibizumab (PRN) | Bromfenac 0.1 % BID (12 m) | 12 m | CFT: −285 µm vs −368 µm | −0.41 vs −0.41 | 2 vs 3.1 |
| YUN 20 | Retro / 68 | Bevacizumab (PRN) | Bromfenac 0.1 % BID (12 m) | 12 m | CFT: −280 µm vs −283 µm | −0.32 vs −0.31 | 5 vs 4.1 |

**1. Diabetic Macular Edema**

- Aqueous suppressants → faster OCT drying, modest injection-sparing, no extra VA gain
- NSAIDs → small thickness drop, no lasting VA or interval benefit

**2. Neovascular AMD**

- Aqueous suppressants → mild extra thinning, a few injections saved, minimal VA change
- NSAIDs & orals → inconsistent anatomical gains, no clear VA or burden relief

**3. RVO-Related Edema**

- Aqueous suppressants → strong extra thinning, ~1 fewer injection, slight VA lift
- NSAIDs → pronounced thinning in BRVO, no reliable VA or interval effect

## Discussion

- **Adjunct** reduces thickness faster (esp. CAIs in early DME & RVO)
- Sustained **VA benefit** not demonstrated in any disease cohort
- **Injection-sparing signal modest**:
  - Nutraceutical AMD (-2 injections / 24 mo)
- **Likely ceiling effect**: After **VEGF suppression**, further drying ≠ visual recovery
- **Safety**:
  - Topical CAIs well-tolerated
  - Steroids ↑ IOP & cataract
  - NSAIDs occasional keratitis
- **Clinical use**: consider **CAI drops or SML** in eyes needing dryer retina / fewer visits but counsel regarding limited VA upside

## Conclusions

- **Anti-VEGF monotherapy** remains the **visual driver**; adjuncts offer incremental anatomical or burden relief.
- **Topical CAIs/β-blockers**: strongest **short-term drying** effect; consider in refractory fluid.
- No current adjunct consistently improves **BCVA**; future combo-molecule or sustained-release strategies might.
- **Clinical implication:** Adjuncts can be considered in refractory fluid cases for **faster OCT resolution** and slight burden relief.

## References

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