Treat and extend regimen of anti-VEGF agents for diabetic macular edema and macular edema secondary to retinal vein occlusion: a meta-analysis

¹Michael DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada; ²Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Ontario, Canada; ³Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; ⁴Department of Ophthalmology, St. Michael's Hospital/Unity Health Toronto, ON, Canada; ⁵Department of Ophthalmology and Vision Sciences, The Hospital for Sick Children, Toronto, ON, Canada; ⁶John and Liz Tory Eye Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Purpose

- Treat-and-extend treatment regimens are commonly used for the treatment of neovascular age-related macular degeneration.
- The safety and efficacy of this regimen relative to others for diabetic macular edema (DME) and macular edema (ME) secondary to retinal vein occlusion (RVO) remains poorly understood.
- This meta-analysis evaluates the comparative safety and efficacy of a treat-and-extend regimen relative to monthly and pro re nata (PRN) regimens using anti-vascular endothelial growth factor (VEGF) agents for DME and ME secondary to RVO.

Methods

- A systematic literature search was conducted on Ovid MEDLINE, EMBASE, and Cochrane Library from inception to December 2021.
- Comparative studies evaluating the efficacy and safety of a treat-and-extend regimen relative to a monthly or PRN regimen with anti-VEGF therapy for DME or ME secondary to RVO were included.
- Other treatment modalities, non-comparative studies, and non-English studies were excluded.
- Cochrane's risk of bias tool 2 and ROBINS-I were used to assess risk of bias and GRADE evaluation was conducted to assess certainty of evidence.
- A random effects meta-analysis was conducted.

- analysis.
- compared to a monthly regimen.
- regimens.

| a) | | Trea | at and Ex | Monthly | | | |
|----|---------------------------------|------------|------------------------|-----------|-----------|-----------------------|---|
| u) | Study or Subgroup | Mear | n SD | Total | Mean | SD | ٦ |
| | Payne 2021 | 74.1 | 6 12.05 | 37 | 71.39 | 10.31 | 1 |
| | Scott 2018 AFL | 71.0 | 6 16.4 | 76 | 72.7 | 17.3 | |
| | Scott 2018 BEV | 7. | 4 14 | 65 | 75.2 | 13.1 | |
| | Total (95% CI) | | | 178 | | | |
| | Heterogeneity: Tau ² | = 0.00; 0 | Chi ^z = 1.3 | 1, df = 2 | 2 (P = 0. | 52); l ² = | 0 |
| | Test for overall effec | t: Z = 0.0 | 06 (P = 0.) | 95) | | | |
| ይ) | | Treat | and Exte | Monthly | | | |
| D) | Study or Subgroup | Mean | SD | Total | Mean | SD | T |
| | Ebneter 2017 | 70.9 | 2.9 | 22 | 66.6 | 2.9 | |
| | Guichard 2018 | 73 | 13 | 32 | 65 | 18 | |
| | Prunte 2016 | 70.39 | 15.312 | 125 | 72.76 | 13.25 | |
| | Tatal (05% CI) | | | 470 | | | |

Total (95% CI) 179 Heterogeneity: Tau² = 17.50; Chi² = 12.06, df = 2 (P = 0.002); l² = 83% Test for overall effect: Z = 0.95 (P = 0.34)

Nikhil S. Patil MD(C),¹ Prem A. H. Nichani MD MSc,² Arjan S. Dhoot BMSc MD(C),³ Marko M. Popovic MD MPH(C),² Rajeev H. Muni MD MSc FRCSC,^{2,4-5} Peter J. Kertes MD CM FRCSC^{2,5-6}

Results

• Seven studies of 984 eyes were included in this

• Relative to a monthly regimen, treat-and-extend was not significantly different for the change in BCVA from baseline to 12 months (p=0.74), 24 months (p=0.39), and final follow-up (p=0.59).

• There was a lower mean number of injections (WMD=-1.54, 95% CI=[-2.01, -1.06], p<0.00001)

• Relative to a PRN regimen, treat-and-extend was not significantly different for final BCVA or change in BCVA from baseline to 12 months (p=0.15; p=0.85), 24 months (p=0.69; p=0.78) and final follow-up (p=0.34; p=0.84), and was associated with a higher mean number of injections (WMD=4.74, 95% CI=[0.83, 8.65], p=0.02).

• There was no difference for safety outcomes between treat-and-extend and monthly or PRN





| 2) | | Treat and Extend | | | Monthly or PRN | | Mean Difference | | | Mean Di | |
|------------|---|------------------|---------|--------|----------------|-----|-----------------|-----------------|----------------------|----------|---------------------|
| a) | Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% Cl | | IV, Rando |
| | Ehlers 2017 | 9.6 | 0.7 | 12 | 10.9 | 0.5 | 15 | 29.4% | -1.30 [-1.77, -0.83] | | |
| | Eichenbaum 2018 | 18.8 | 2.9 | 10 | 19.4 | 5.9 | 10 | 1.3% | -0.60 [-4.67, 3.47] | | 1 |
| | Scott 2018 AFL | 3.8 | 1.2 | 76 | 5.8 | 0.7 | 78 | 35.1% | -2.00 [-2.31, -1.69] | | |
| | Scott 2018 BEV | 4.5 | 1.2 | 65 | 5.8 | 0.7 | 66 | 34.2% | -1.30 [-1.64, -0.96] | | |
| | Total (95% CI) | | | 163 | | | 169 | 100.0% | -1.54 [-2.01, -1.06] | | • |
| | Heterogeneity: Tau ² = 0.14; Chi ² = 11.18, df = 3 (P = 0.01); l ² = 73% | | | | | | | | | <u> </u> | |
| | Test for overall effect | Z= 6.36 (| P < 0.0 | 00001) | | | | | | -10 | -5 Favours [T&E] |
| b) | | Treat and Extend | | | Monthly or PRN | | | Mean Difference | | Mean D | |
| | Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% Cl | | IV, Rando |
| | Ebneter 2017 | 8.9 | 2 | 22 | 5.9 | 1.8 | 24 | 33.7% | 3.00 [1.90, 4.10] | | |
| | Guichard 2018 | 15 | 3.1 | 32 | 5.8 | 2.7 | 24 | 32.9% | 9.20 [7.68, 10.72] | | |
| | Prunte 2016 | 12.8 | 3.7 | 125 | 10.7 | 5.6 | 117 | 33.5% | 2.10 [0.90, 3.30] | | |
| | Total (95% CI) | | | 179 | | | 165 | 100.0% | 4.74 [0.83, 8.65] | | |
| | Heterogeneity: Tau ² = 11.51; Chi ² = 57.46, df = 2 (P < 0.00001); l ² = 97% | | | | | | | | | | <u> </u> |
| | Test for overall effect | Z= 2.37 (| P = 0.0 |)2) | | | | | | -10 | -5 Favours (T&E) |

Figure 2. Number of injections for treat-and-extend compared to a) monthly and b) PRN regimens.

Discussion

- This meta-analysis found that a treat-and extend regimen was non-inferior to monthly and PRN treatment regimens in efficacy and safety endpoints for the management of DME or ME secondary to RVO.
- There was a significantly greater injection frequency of a treat-and-extend regimen relative to a PRN protocol, and significantly lesser injection frequency relative to a monthly regimen.
- Overall, there is a paucity of literature in this domain and further investigation is warranted.

Conflicts of Interest

N.P: None Declared, P.N: None Declared, A.D: None Declared, M.P: PSI Foundation, R.M: Bayer, Novartis, P.K: Bayer, Roche, Novartis, ArcticDx







