

Treat-and-Extend Regimens for the Management of Neovascular Age-related Macular Degeneration and Polypoidal Choroidal Vasculopathy: Consensus and Recommendations From the Asia-Pacific Vitreo-retina Society

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Purpose: Review and provide consensus recommendations on use of treat-and-extend (T&E) regimens for neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV) management with relevance for clinicians in the Asia-Pacific region.

Methods: A systematic search of MEDLINE, EMBASE, and Cochrane databases, and abstract databases of the Asia-Pacific Vitreo-retina Society, European Society of Retina Specialists, American Academy of Ophthalmology, and Controversies in Ophthalmology: Asia-Australia congresses, was conducted to assess evidence for T&E regimens in nAMD. Only studies with ≥ 100 study eyes were included. An expert panel reviewed the results and key factors potentially influencing the use of T&E regimens in nAMD and PCV, and subsequently formed consensus recommendations for their application in the Asia-Pacific region.

Results: Twenty-seven studies were included. Studies demonstrated that T&E regimens with aflibercept, ranibizumab, or bevacizumab in nAMD, and with aflibercept in PCV, were efficacious and safe. The recommendation for T&E is, after ≥ 3 consecutive monthly loading doses, treatment intervals can be extended by 2 to 4 weeks up to 12 to 16 weeks. When disease activity recurs, the recommendation is to reinject and shorten intervals by 2 to 4 weeks until fluid resolution, after which treatment intervals can again be extended. Intraretinal fluid should be treated until resolved; however, persistent minimal subretinal fluid after consecutive treatments may be tolerated with treatment intervals maintained or extended if the clinical condition is stable.

Conclusions: T&E regimens are efficacious and safe for nAMD and PCV, can reduce the number of visits, and minimize the overall burden for clinicians and patients.

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Neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV) are major causes of vision loss in aging individuals globally.^{1–5} For nAMD, the current standard of care is intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents.^{3,5–7} For PCV, which is more common in Asian patients compared with non-Asian patients,^{8–10} the standard of care is also intravitreal anti-VEGF injections, although there are situations that may require the addition of verteporfin photodynamic therapy.^{7–9,11–14}

Over the past decade, major clinical trials and real-world studies worldwide have demonstrated the efficacy and safety of intravitreal anti-VEGF agents for the treatment of nAMD and PCV.^{12,15–21} Typically, 3 main approaches for the administration of intravitreal anti-VEGF injections are employed: fixed dosing regimens, “reactive” *pro re nata* (PRN) dosing regimens (ie, treatment on an as-needed basis), and “proactive” treat-and-extend (T&E) dosing regimens.³ Fixed dosing regimens require continuous monthly or bimonthly injections for at least 1 year.^{15–17} A PRN regimen requires monthly monitoring visits, with treatment reinstated when disease activity recurs.^{3,22} A T&E regimen is typically initiated with ≥ 3 consecutive monthly injections until disease inactivity is established, followed by gradual extension of the treatment interval in increments of 2 to 4 weeks, up to a maximum interval of 12 to 16 weeks. Treatment intervals are shortened when disease activity recurs. Anti-VEGF injections are given at every scheduled visit despite disease inactivity.^{3,20,23–27}

Increasingly, T&E is the preferred option for clinicians globally because it allows the extension of treatment intervals while reducing the overall number of clinic visits.^{25,28} In the Asia-Pacific region, T&E could play a particularly important role as the majority of populations live in countries with limited health care access, and many patients must commute vast distances to major treatment centers which may adversely affect treatment compliance. Studies suggest poor treatment adherence and suboptimal visual outcomes are correlated with infrequent clinic visits, due to difficulties with transportation along with direct and indirect out-of-pocket patient payments for each visit in these self-pay markets.²⁹

Currently, there are few guidelines on the use of T&E in the Asia-Pacific region.⁵ To address this gap, this publication aims to review related literature and provide consensus recommendations from a group of experts on the use of T&E for the management of nAMD and PCV in the Asia-Pacific region.

METHODS

Step 1: Systematic Literature Review

Inclusion Criteria and Search Strategy

We conducted a systematic search of the MEDLINE, EMBASE, and Cochrane databases, in addition to abstracts from the Asia-Pacific Vitreo-retina Society (APVRS), European Society of Retina Specialists (EURETINA), American Academy of Ophthalmology (AAO), and Controversies in Ophthalmology: Asia-Australia (COPHy AA) congresses, to identify studies that

assessed T&E regimens using aflibercept, ranibizumab, and bevacizumab in patients with nAMD. Database searches were limited to studies published up to October 2020 (no specific start date), and congress searches were limited to abstracts published between January 2019 and November 2020. Our search strategy followed the PRISMA checklist for systematic reviews and meta-analyses, and appropriate studies were selected based on the inclusion criteria in Supplementary Digital Content, Table 1, <http://links.lww.com/APJO/A113>. Eligible study designs included randomized controlled trials (RCTs), observational case-control or cohort studies, and systematic literature reviews with or without meta-analyses. Only studies that assessed ≥ 100 study eyes of adult patients (≥ 18 years of age) with a diagnosis of nAMD were included in the analysis. Studies of patients with a diagnosis of diabetic macular edema or retinal vein occlusion, or mixed populations where nAMD subgroups were not reported separately, were excluded from this analysis.

Study Selection

The titles, abstracts, and full text of all identified articles were screened by 2 independent researchers to ensure that the studies matched the inclusion criteria. A third reviewer made the final decision on inclusion in instances where the 2 researchers searching could not reach an agreement. The flowchart showing the article selection process is depicted in Figure 1.

Data Extraction

Data extraction was performed on eligible full-text, peer-reviewed publications and on eligible abstracts from the congress databases to obtain the following information: study design, study participants, interventions, and comparators; and key outcomes of interest, including changes in best-corrected visual acuity (BCVA) from baseline to end of study, injection intervals, and the number of intravitreal injections and clinic visits over the study period.

Step 2: Obtaining Consensus From an Expert Panel

An expert panel comprising 18 international medical retina specialists representing the APVRS met online and reviewed the results of Step 1. No studies comparing the use of T&E regimens with anti-VEGF agents in patients with PCV that would meet the inclusion criterion for ≥ 100 study eyes were known to the panel at the time of the initial literature review; thus, PCV was not included in the systematic search. Since the initial review, new evidence for T&E in PCV was available in the literature, and was collected through a separate search of online databases and reviewed separately by the expert panel. Subsequently, the panel convened online to discuss the key factors that may influence use of T&E regimens for the management of nAMD and PCV in the Asia-Pacific region, including drug efficacy and safety, molecular properties, and fluid types in the retina. Consensus recommendations for T&E implementation were developed and agreed upon by each member of the expert panel (Fig. 2).

RESULTS

Part 1: Results of the Systematic Literature Review

Overall, 393 potentially relevant unique publications were identified using the search parameters stated previously. Of these,

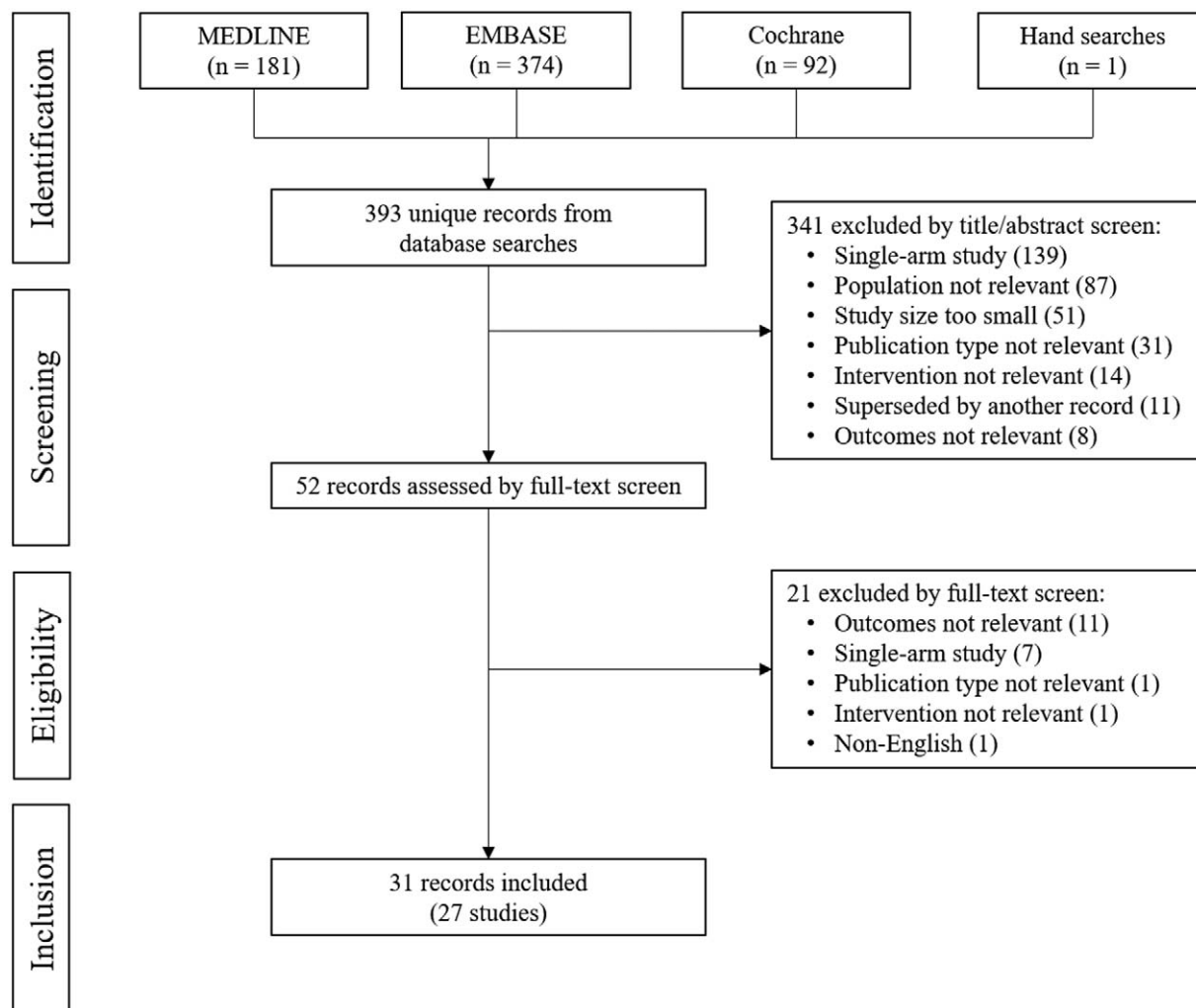


FIGURE 1. PRISMA flowchart for the article selection process in this systematic review.

341 were excluded during title/abstract screening and 52 were eligible for full-text screening. Overall, 27 studies from 31 publications were included: 8 RCTs, 14 observational case-control or cohort studies, and 5 meta-analyses. The overall study characteristics (including diagnosis, anti-VEGF agents, and treatment regimen comparison) are shown in Table 1. The study design, study duration, visual outcomes (eg, change in BCVA from baseline), treatment interval, and number of injections and/or clinic visits of each study are detailed in Supplementary Digital Content, Table 2, <http://links.lww.com/APJO/A114>.

Visual Outcomes

Results from the TREND²⁷ and CANTREAT^{26,30} trials, the only 2 head-to-head RCTs comparing T&E vs fixed monthly dosing regimens in patients with nAMD, suggested that visual outcomes were comparable in both groups. Mean change in BCVA from baseline in the ranibizumab T&E and monthly arms was +6.2 vs +8.1 letters, respectively ($P < 0.001$ for noninferiority), at Year 1 in TREND,²⁷ and +6.8 vs +6.0 letters, respectively ($P = 0.21$), at Year 2 in CANTREAT.²⁶

The ARIES trial comparing early-start T&E (T&E starting in Year 1) and late-start T&E (bimonthly dosing in Year 1, followed by T&E in Year 2) reported a comparable mean change in BCVA in both groups from randomization at Week 16 to Week 52 (+0.9

vs +1.1 letters, respectively).³¹ An observational study by Almuhtaseb et al³² assessed visual outcomes with ranibizumab T&E and aflibercept bimonthly dosing, reporting comparable BCVA gains from baseline to Month 12 (+8.3 vs +7.5 letters, respectively; $P = 0.1550$).

The In-Eye trial, an RCT that compared ranibizumab T&E and bimonthly dosing regimens with PRN, found that T&E and bimonthly dosing were noninferior to PRN for mean change in BCVA at Month 12 (+6.4, +7.2, and +8.0 letters, respectively).³³ However, the 8 observational studies and 2 meta-analyses that evaluated T&E vs PRN regimens reported a relatively higher mean gain in BCVA from baseline with T&E than with PRN.^{24,34–43}

Four RCTs compared T&E regimens and reported comparable visual outcomes between different T&E protocols (ALTAIR,²⁰ FLUID²³) and between different agents (LUCAS,⁴⁴ RIVAL⁴⁵). Two observational studies reported similar mean changes in BCVA from baseline with aflibercept and ranibizumab T&E regimens over the study period.^{46,47}

Number of Injections and Clinic Visits

Compared with fixed monthly dosing, T&E regimens typically required fewer injections over the study period. In the TREND trial, the mean number of injections in Year 1 with

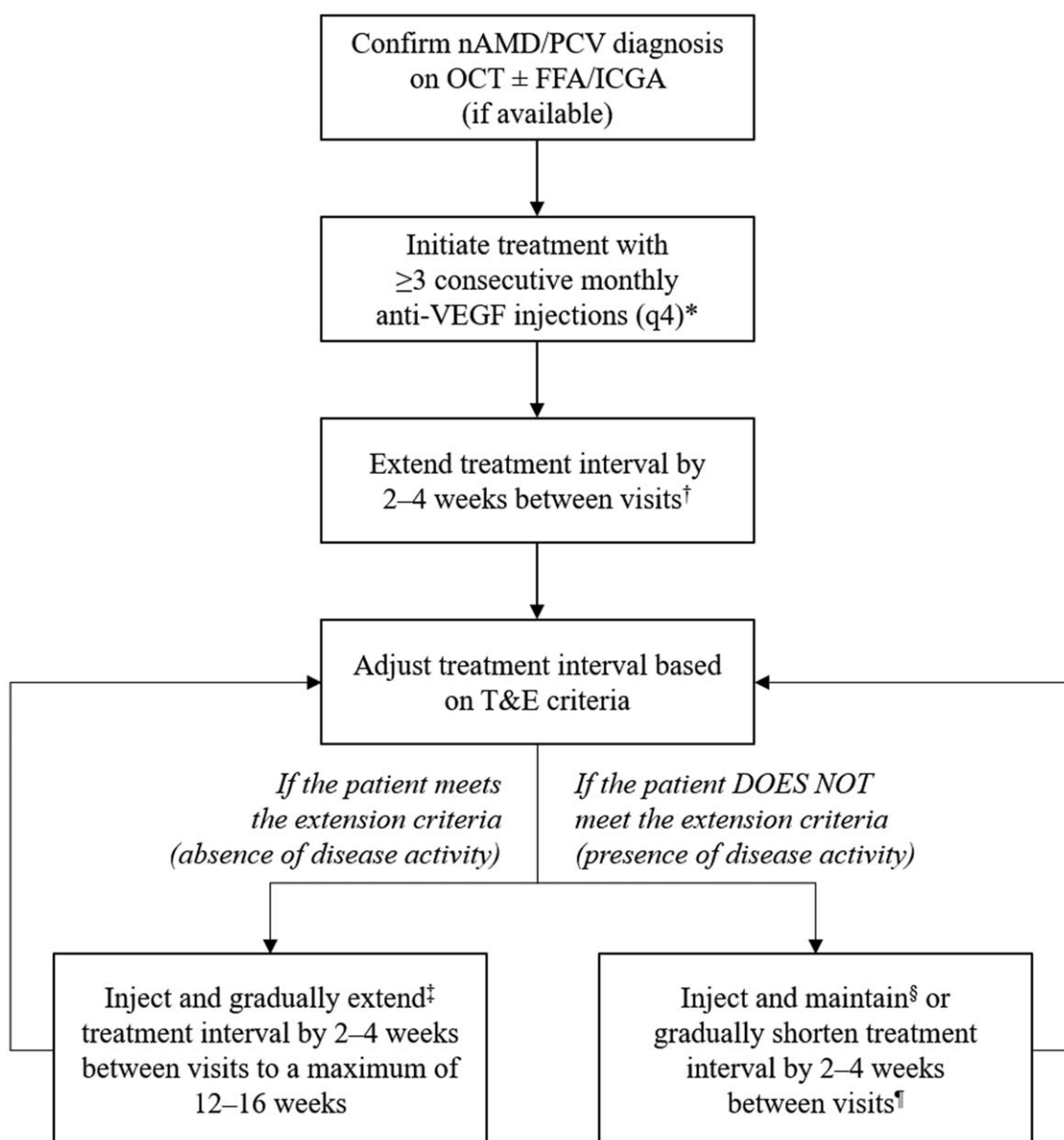


FIGURE 2. Flowchart of recommendations for implementation of a T&E regimen for the treatment of patients with nAMD/PCV in the Asia-Pacific region. *At least 3 consecutive monthly injections until maximum VA is achieved and/or there are no signs of disease activity. †When using ranibizumab or bevacizumab, extend by 2 weeks; when using aflibercept, extend by 2–4 weeks. ‡Extend at the physician's discretion if visual and anatomic criteria for extension are met. Aflibercept: gradually extend in 2- or 4-week increments up to a maximum of 16 weeks; ranibizumab/bevacizumab: gradually extend by 2 weeks at a time up to a maximum of 12 weeks. §An interval maintenance step (such as that used in ALTAIR) may be implemented, permitting tolerance of some residual SRF when vision has improved or remained stable and there are no signs of disease worsening (such as new subretinal hemorrhage)²⁰. ¶Shorten at the physician's discretion if visual and anatomic criteria for shortening are met; that is, vision has worsened and/or there are signs of disease worsening (such as recurrence of IRF regardless of recurrent/residual SRF). FFA indicates fundus fluorescein angiography; ICGA, indocyanine green angiography; IRF, intraretinal fluid; nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; PCV, polypoidal choroidal vasculopathy; q4, every 4 weeks; SRF, subretinal fluid; T&E, treat-and-extend; VA, visual acuity; VEGF, vascular endothelial growth factor.

ranibizumab T&E and monthly ranibizumab dosing was 8.7 vs 11.1, respectively.²⁷ In the CANTREAT trial, the ranibizumab T&E and monthly ranibizumab arms received 9.4 vs 11.8 injections in Year 1, and 17.6 vs 23.5 over 2 years, respectively ($P < 0.001$).^{26,30}

The In-Eye trial reported a greater mean number of injections and clinic visits with ranibizumab T&E compared with bimonthly dosing over 12 months (injections: 9.3 vs 7.6; visits: 10.4 vs 8.6, respectively; $P < 0.001$).³³ In the ARIES trial, the early-start T&E arm received approximately one fewer injection over 12 months than the late-start T&E arm.³¹ This difference was also reflected over 2 years of the ARIES study, with patients in the late-start

T&E arm switching to a T&E regimen in the second year.¹⁸ Almuhtaseb et al³² reported comparable injection numbers over 12 months with ranibizumab T&E and aflibercept bimonthly dosing in an observational study.

Compared with PRN dosing, T&E typically required more injections but fewer clinic visits over 12 months. In the In-Eye trial, a mean of 9.3 vs 7.4 injections were administered in the ranibizumab T&E and PRN arms, respectively ($P < 0.001$), with a mean of 10.4 vs 13.6 clinic visits over 12 months ($P < 0.001$).³³ The number of injections with T&E regimens may decrease in subsequent years; however, a head-to-head RCT comparing T&E with PRN strategies beyond 1 year is not yet available. Seven

TABLE 1. Overall Characteristics of the Studies Included in This Systematic Review

Characteristic	RCT	Observational Study	Meta-analysis
Number of studies	8	14	5
Diagnosis:			
nAMD	8	14	5
PCV	1*	1*	2†
Intervention:			
Aflibercept	3	7	2
Bevacizumab	1	—	1
Ranibizumab	6	11	4
Anti-VEGF (unspecified)	—	3	1
Treatment regimen comparison:			
T&E vs fixed monthly	2	—	2
T&E vs fixed bimonthly	1	3	—
T&E vs PRN	1	8	2
T&E vs T&E	5	4	2
T&E vs other / unspecified non-T&E	—	2	—

*Study included patients with PCV diagnosis at baseline.

†Two meta-analyses report including studies of patients with PCV diagnosis.

nAMD indicates neovascular age-related macular degeneration; PCV, polypoidal choroidal vasculopathy; PRN, *pro re nata* (as needed); RCT, randomized controlled trial; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

observational studies comparing T&E with PRN regimens reported more injections over the study period with T&E than with PRN^{24,36,39–43}; however, of these studies, the 3 that reported number of clinic visits indicated more visits with PRN than with T&E regimens.^{24,40,42} Similarly, both meta-analyses that evaluated T&E and PRN regimens reported more injections but fewer clinic visits, on average, with T&E than with PRN over 12 months.^{34,35}

Four RCTs compared T&E regimens, reporting comparable injection numbers between different T&E protocols (ALTAIR,²⁰ FLUID²³) and between agents (LUCAS,⁴⁴ RIVAL⁴⁵). Three observational studies reported similar numbers of injections with aflibercept and ranibizumab T&E regimens over the study period.^{42,46,47} In a network meta-analysis and indirect comparison, Ohji et al⁴⁸ reported that patients receiving aflibercept T&E achieved and maintained visual improvements with approximately 6 fewer injections over 2 years compared with those receiving ranibizumab T&E.

T&E Treatment Intervals

Traditional T&E regimens allowed adjustment of treatment intervals by 2 weeks, up to a maximum of 12 weeks, as demonstrated with ranibizumab or aflibercept across many studies.^{18,20,24,26,27,44,45} The ALTAIR trial, which evaluated 2 aflibercept T&E regimens in patients with nAMD (and a subgroup of around 37% diagnosed with PCV), demonstrated a more flexible T&E regimen approach in which treatment intervals were adjusted by 2 or 4 weeks up to a maximum possible interval of 16 weeks. In ALTAIR, 56.9% to 60.2% of patients achieved treatment intervals of ≥ 12 weeks and 41.5% to 46.3% achieved intervals of 16 weeks by Week 96. Moreover, 77.6% to 96.3% of patients who reached the maximum possible treatment interval of 16 weeks were maintained at this interval to Week 96.²⁰

Variability of T&E Retreatment Criteria: Fluid Compartments

Fourteen of 22 studies assessing a T&E regimen (excluding meta-analyses) employed a traditional T&E regimen requiring

complete resolution of both intraretinal fluid (IRF) and subretinal fluid (SRF) on optical coherence tomography (OCT) as a definition for “inactive disease” to allow extension of the treatment interval. These studies were the CANTREAT,^{26,30} In-Eye,³³ LUCAS,^{44,49} RIVAL,^{45,50} TREND²⁷ trials, and many observational studies.^{24,32,37,39,42,43,46,51} However, FLUID,²³ ALTAIR,²⁰ and ARIES^{18,31} and 2 observational studies,^{41,47} have indicated the potential for vision gains with a T&E regimen without the need to aim for complete fluid resolution. In the FLUID trial, patients receiving a ranibizumab T&E regimen that tolerated the presence of ≤ 200 μm SRF for extending the treatment interval had comparable outcomes to patients receiving traditional T&E that required complete resolution of fluid (Table 2).²³ In the ALTAIR trial, patients receiving an aflibercept T&E regimen that permitted the maintenance of the treatment interval in the presence of some residual but decreased fluid from the previous visit gained up to +7.6 letters from baseline at Week 96.²⁰ Use of an interval maintenance step has not yet been assessed with ranibizumab T&E regimens. Two-year results from ARIES reported vision gains of +4.3 and +7.9 letters from baseline at Week 104 with an aflibercept T&E regimen starting in either Year 1 or Year 2, respectively, that permitted the presence of ≤ 50 μm SRF as a criterion for extending treatment intervals up to 16 weeks.¹⁸

Safety

No new safety concerns were reported on the use of T&E regimens with intravitreal aflibercept, ranibizumab, and off-label bevacizumab injections.

Part 2: Consensus From an Expert Panel

Role of T&E in the Asia-Pacific Region

The high costs of treatment and high frequency of clinic visits required for nAMD and PCV management have burdened health care systems in the Asia-Pacific region. Despite an increasing number of patients with nAMD and PCV in this region,² many countries have limited health care personnel and resources, and, unlike in many western countries such as France and Germany

TABLE 2. Study Criteria and Outcomes Across RCTs of Afibercept, Ranibizumab, and Bevacizumab With a T&E Regimen

Study Criteria and Outcomes	Afibecept® (ALTAIR, n = 246) ²⁰	Afibecept® (ARIES, n = 210) ^{18,31}	Afibecept® (RIVAL, n = 137) ^{45,50}	Ranibizumab [†] (RIVAL, n = 141) ^{45,50}	Ranibizumab [†] (TREND, n = 290) ²⁷	Ranibizumab [†] (CANTREAT, n = 237) ²⁶	Ranibizumab [†] (FLUID relaxed, n = 173) ²³	Ranibizumab [†] (FLUID intensive, n = 172) ²³	Ranibizumab [†] (In-Eye, n = 99) ³³	Ranibizumab [†] (LUCAS, n = 172) ^{44,49}	Bevacizumab [‡] (LUCAS, n = 167) ^{44,49}
Diagnosis	nAMD, PCV	nAMD	nAMD	nAMD	nAMD	nAMD	nAMD	nAMD	nAMD	nAMD	nAMD
Primary endpoint	Mean change in BCVA from baseline at Week 52	Mean change in BCVA from Week 16 to Week 104	Mean change in square root area of MA	Mean change in square root area of MA	Mean change in BCVA from baseline at Week 52	Mean change in BCVA from baseline at Week 52	Mean change in BCVA from baseline at Week 52	Mean change in BCVA from baseline at Week 52	Mean change in BCVA from baseline at Week 52	Mean change in BCVA from baseline at Week 52	Mean change in BCVA from baseline at Week 52
Duration, months	24	24	24	24	12	24	24	24	12	24	24
Randomized group comparison(s)	T&E vs T&E	T&E vs T&E	T&E vs T&E	T&E vs T&E	T&E vs monthly	T&E vs monthly	T&E vs T&E	T&E vs T&E	T&E vs bimonthly vs PRN	T&E vs T&E	T&E vs T&E
Tolerance of increase in retinal fluid	CRT ≤100 μm	SRF ≤50 μm	Zero fluid tolerance	Zero fluid tolerance	Zero fluid tolerance	Zero fluid tolerance	SRF ≤200 μm	Zero fluid tolerance	Zero fluid tolerance	Zero fluid tolerance	Zero fluid tolerance
Option to maintain treatment interval	✓	×	×	×	×	×	×	×	×	×	×
Mean change in BCVA from baseline, letters	+6.1 to +7.6	+4.3 to +7.9	+5.2	+6.9	+6.2	+6.8	+2.6	+3.0	+6.7	+6.6	+7.4
Patients extended to ≥q12, %	56.9 to 60.2	47.2 to 51.9	31	32	22.3	43.1	29.6	15.0	NR	17.0	10.0
Patients extended to q16, %	41.5 to 42.3	26.9 to 30.2	—§	—§	—§	—§	—§	—§	—§	—§	—§
Mean number of injections	10.4	12.5	17.0	17.7	8.7	17.6	15.8	17.0	9.3	16.0	18.2

Please note that this information is from separate, independent studies and therefore should be interpreted carefully; no direct comparisons should be made. Clinical trial numbers for the studies are: ALTAIR (NCT02305238), ARIES (NCT02581891), RIVAL (NCT02130024), TREND (NCT01948830), CANTREAT (NCT01972789), In-Eye (EudraCT: 2012-003431-37), and LUCAS (NCT01127360).

*2.0 mg.

†0.5 mg.

‡1.25 mg.

§The maximum treatment interval in this study was 12 weeks.

BCVA indicates best-corrected visual acuity; CRT, central retinal thickness; EudraCT, European Union Drug Regulating Authorities Clinical Trials Database; IRF, intraretinal fluid; MA, macular atrophy; nAMD, neovascular age-related macular degeneration; NR, not reported; PCV, polypoidal choroidal vasculopathy; PRN, *pro re nata* (as needed); q12, every 12 weeks; q16, every 16 weeks; RCT, randomized controlled trial; SD, standard deviation; SRF, subretinal fluid; T&E, treat-and-extend.

where national health insurance systems provide full coverage for all anti-VEGF treatments, reimbursement policies are often restricted (eg, limited number of anti-VEGF injections per eye or per patient) or treatment is often not covered by government health insurance systems.^{52–54} In addition, a number of patients face difficulties with transportation between home and the clinic, and inability to afford frequent clinic visits because of low socioeconomic status, especially those living in developing countries and rural areas. Therefore, fixed monthly and PRN dosing regimens that require monthly clinic visits may be considered impractical from the perspective of clinicians and patients. A T&E regimen offers advantages of extending treatment intervals and reducing number of clinic visits, with comparable or favorable visual outcomes compared with other treatment regimens.^{5,25} Thus, the principle of T&E, where “every visit is a treatment visit” is appealing for patients in the Asia-Pacific region.

T&E Regimens for PCV

In addition to the results of Part 1 from studies of patients with nAMD, several studies investigating the efficacy of aflibercept monotherapy have demonstrated that T&E regimens are also suitable for patients with PCV (Supplementary Digital Content, Table 3, <http://links.lww.com/APJO/A115>).^{7,13,55–60} In the PLANET trial, investigators had the option to treat according to a T&E regimen in Year 2. Overall, 41.2% of patients with PCV achieved treatment intervals of ≥ 12 weeks with VA gains of >10 letters maintained up to Year 2.^{7,13} In the ALTAIR trial, a subgroup of patients with PCV (around 37%) achieved VA gains of up to +4.9 letters by Week 96, with a similar proportion of patients extended to treatment intervals of ≥ 12 weeks as in the overall cohort (up to 62.8% vs up to 60.2%, respectively).^{20,61} To our knowledge, there are currently no head-to-head RCTs comparing different anti-VEGF agents with T&E regimens in PCV.

In a prospective study by Maruko et al⁶⁰ exploring 2-year outcomes with aflibercept T&E, vision in patients with PCV had improved by 0.13 logMAR units (approx. +6.5 ETDRS letters) at Year 2. These patients received fewer injections compared with an nAMD cohort over 2 years (12.0 vs 14.3, respectively; $P < 0.01$), with 67.3% vs 51.1% of patients with PCV and nAMD, respectively, maintained at 12-week intervals.⁶⁰

In a recent RCT of 53 patients with PCV, Teo et al⁵⁹ demonstrated that an individualized aflibercept T&E regimen was noninferior to fixed bimonthly dosing for mean change in BCVA from baseline at Week 52 (+8.1 vs +7.9 letters, respectively; $P = 0.86$), with 47.4% in the T&E arm achieving a last treatment interval of 12 weeks. Complete polypoidal regression was achieved at Week 52 in 55.2% and 41.6% of patients in the T&E and bimonthly arms, respectively; however, this difference was not statistically significant ($P = 0.41$).⁵⁹

Several real-world studies have also demonstrated the effectiveness of aflibercept T&E in patients with PCV, with reported VA gains of up to +9.0 letters at Year 2⁵⁵ and approximately half of the patients (45.9% to 55.2%) experiencing complete polypoidal regression after the loading phase.^{55,57,58} Moreover, Hosokawa et al⁵⁸ and Tamachi et al⁵⁶ reported that 59.5% and 60.8% of patients, respectively, were maintained on treatment intervals of ≥ 12 weeks at Year 1, and Morizane-Hosokawa et al⁵⁵ reported that 47.3% of patients had reached 16-week intervals at Year 2.

Recommendations for Implementation of T&E Regimens

Each member of the panel agreed on the following recommendations. After a diagnosis of nAMD or PCV, at least 3 consecutive monthly intravitreal anti-VEGF injections should be given until disease inactivity (ie, no new hemorrhage or no fluid on OCT) is observed to allow maximum vision gains and a stable macular status. When using ranibizumab (or off-label bevacizumab), the treatment interval can then be extended by 2 weeks between visits up to 12-week intervals^{23,27,30,44}; when using aflibercept, the treatment interval can be extended by 2 to 4 weeks between visits up to 16-week intervals.^{18,20} Anti-VEGF injections should be given at every visit despite disease inactivity. When disease activity recurs (ie, presence of IRF and/or SRF on OCT), an injection should be given and the treatment interval shortened by 2 to 4 weeks until IRF and/or SRF resolve(s). In cases of severe disease reactivation, that is, massive subretinal / sub-retinal pigment epithelium (sub-RPE) hemorrhage and/or worsening VA (≥ 15 -letter loss), the treatment interval can be instantly reduced to every 4 weeks, even if the previous interval was 12 to 16 weeks. Upon achieving disease inactivity, the treatment interval can be gradually extended by 2 to 4 weeks, depending on the anti-VEGF agent, again until the patient has reached the previous longest interval without reactivation. A second attempt to extend beyond the previous threshold can be considered; however, if reactivation occurs after the second attempt, further attempts are unlikely to be successful. Importantly, regarding disease activity assessment, IRF should be aggressively treated until resolved, but small amounts of SRF (ie, $\leq 200 \mu\text{m}$ subfoveal fluid) may be tolerated if it cannot be eliminated after at least 2 consecutive treatments and there are no other indicators of disease activity. For example, for an eye that has been successfully extended to 8-week intervals following loading but develops SRF at 10-week intervals (first failed extension), the interval should be shortened from 10 weeks to 8 weeks. Upon resolution of SRF following the shortening, a second attempt to extend to 10 weeks can be considered. If only SRF recurred, and vision remains stable without other evidence of disease activity (such as IRF or retinal hemorrhage), this SRF may be tolerated and the 10-week treatment interval can be maintained, providing the amount of SRF does not increase further in subsequent visits. In cases where IRF persists despite multiple periods of high-frequency dosing, that is, every 4 weeks, it is important to differentiate the exudative IRF from the degenerative IRF based on the morphology of the intraretinal cyst and the underlying RPE structure.⁶² In the absence of exudative IRF or SRF, eyes with persistent degenerative IRF (seen as small, sharply demarcated hyporeflective spaces in the inner retina overlying areas of RPE atrophy or scarring) might be considered for treatment discontinuation when disease is stable rather than receiving monthly injections indefinitely. The panel’s recommendations for implementation of a T&E regimen are shown in Figure 2 and summarized in Table 3.

The durability of anti-VEGF agents may depend on their molecular properties, including potency, VEGF binding affinity, and intravitreal half-life.^{63–65} The known molecular properties of available anti-VEGF agents, including brodalumab (a novel, single-chain antibody fragment with the smallest molecular weight of the available intravitreal anti-VEGF agents), are summarized in Supplementary Digital Content, Table 4, <http://links.lww.com/APJO/A116>.^{63,64,66–70} Given the reported differences

TABLE 3. Summary of Consensus Recommendations of T&E Regimens for nAMD/PCV

Initiation Phase	Maintenance Phase and Interval Adjustments	Fluid Compartment Considerations
Following nAMD or PCV diagnosis, at least 3 consecutive monthly intravitreal anti-VEGF injections should be given until no disease activity (ie, new hemorrhage or fluid on OCT) is observed	<ul style="list-style-type: none"> If no disease activity is observed at FU visits: when using ranibizumab or bevacizumab, inject and extend treatment interval by 2 weeks between visits up to 12 weeks; when using aflibercept, inject and extend treatment interval by 2–4 weeks between visits up to a maximum interval of 16 weeks If disease activity is observed, inject and shorten the treatment interval by 2–4 weeks, until IRF and/or SRF are not observed, then the treatment interval can be gradually extended 	<ul style="list-style-type: none"> IRF should always be treated until resolved For persistent residual SRF despite continuous anti-VEGF injections, subfoveal fluid of $\leq 200 \mu\text{m}$ may be tolerated and the treatment interval could be maintained or gradually extended by 2–4 weeks, depending on the anti-VEGF agent, if vision is stable and there are no signs of disease worsening

FU indicates follow-up; IRF, intraretinal fluid; nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; PCV, polypoidal choroidal vasculopathy; SRF, subretinal fluid; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

in durability (ie, the potential for achieving extended treatment intervals) of each anti-VEGF agent with a T&E regimen in our investigation, with ranibizumab the treatment interval may be extended stepwise by no more than 2 weeks at a time (until signs of disease activity or visual impairment recur) up to a maximum of 12 weeks. To our knowledge, extension of the treatment interval in 4-week increments between visits and treatment intervals of >12 weeks have not been assessed in clinical trials of ranibizumab T&E.^{26,27,30,33,44,49} Based on evidence from the ALTAIR and ARIES trials, the treatment interval with aflibercept T&E may be gradually extended in 2- or 4-week increments up to a maximum of 16 weeks.^{18,20}

Overall, we recommend that extended treatment intervals should be considered on a case-by-case basis, considering drug properties, retinal fluid patterns, disease type, and patient characteristics.

Recommendations for Stopping Treatment

There is currently no level 1 evidence in the literature regarding stopping anti-VEGF treatment for nAMD and PCV (ie, who, when, how). Clinical experience from the panel suggests anti-VEGF therapy may be discontinued in some patients on a case-by-case basis after careful discussion with patients. Specifically, patients should be counseled regarding the increased risk of disease reactivation that may lead to irreversible vision loss.

Based on the chronicity of nAMD and PCV, the panel suggests it may be reasonable to attempt discontinuing injections in patients with stable inactive disease who have received treatments at 16-week intervals for a few consecutive visits (eg, two 16-week intervals) to avoid lifelong injections. After discontinuation, patients should be advised to regularly self-monitor for symptoms of declining vision. Scheduled monitoring visits are crucial for detecting early recurrences and for monitoring the fellow eye status.⁴ Additionally, treatment discontinuation can be considered in patients with advanced nAMD/PCV with substantial scarring and/or atrophy (ie, medical futility).⁷¹ For PCV, eyes with incomplete polypoidal regression should be cautiously monitored when treatment is discontinued, as these have higher chances for recurrent massive subretinal hemorrhage with declining vision.^{72–74}

DISCUSSION

It is estimated that by 2050 the number of people aged 65 or above will be over 1.5 billion worldwide, with the largest

increases occurring in the Asia-Pacific region.⁷⁵ Despite an increasing number of patients with nAMD and PCV in this region, many patients face barriers to accessing adequate treatment, in particular those living in developing countries or rural areas.²⁹

Current evidence indicates that proactive T&E regimens have the potential to optimize patient outcomes and minimize the number of clinic visits in patients with nAMD and PCV.^{4,18,20} The TREND²⁷ and CANTREAT^{26,30} trials suggested that vision gains in patients receiving ranibizumab T&E were comparable to those in patients receiving fixed monthly dosing; however, T&E required fewer injections, and therefore clinic visits, than monthly dosing to achieve comparable outcomes.^{26,30} Compared with PRN regimens (which require monthly monitoring visits), a T&E regimen provides comparable or relatively greater visual improvements. Although T&E regimens typically require more injections than PRN dosing over the first 12 months, fewer clinic visits are required with T&E in the following years.^{24,33,40,42} Moreover, the ALTAIR²⁰ and ARIES¹⁸ trials and several observational studies have indicated that the frequency of aflibercept injections with T&E regimens can notably decrease in subsequent years of treatment while maintaining vision gains achieved in the first year, further highlighting the benefits of T&E for reducing treatment burden on patients and health care systems.^{18,20,76–78} Therefore, the APVRS expert panel recommends the use of T&E regimens for the management of patients with nAMD and PCV in the Asia-Pacific region, with advantages of reducing the burden of frequent clinic visits and providing certainty of scheduled treatment visits while still providing meaningful visual outcomes for patients.

The consensus recommendations for implementation of a T&E regimen with aflibercept allow interval adjustment by 2 to 4 weeks with extension up to 16 weeks based on the findings of the ALTAIR trial, which is different from traditional T&E regimens that allowed interval adjustment by no more than 2 weeks with extension up to 12 weeks.^{26,27,30,44,49} The 96-week results of the ALTAIR trial showed that 46% of patients receiving aflibercept T&E can be extended to the maximum possible treatment interval of 16 weeks without compromising visual outcomes. Up to 96.3% of patients who reached intervals of 16 weeks were maintained at this interval to Week 96, highlighting the potential longevity of the T&E approach with aflibercept.²⁰ This modified T&E approach that allows longer intervals between follow-up visits might potentially help decrease the burden of clinic visits in the future.

The consensus recommendations also provide flexible retreatment criteria that permit the presence of minimal, persistent subfoveal fluid of $\leq 200 \mu\text{m}$ based on the recent findings from the FLUID study. While the FLUID²³ study did not include patients diagnosed with PCV, ALTAIR²⁰ (which permitted tolerance of some residual stable fluid as a criterion for maintaining the current treatment interval) did include some patients with PCV. Taken together, evidence from the FLUID,^{23,79} ALTAIR²⁰ and ARIES¹⁸ studies suggested that some residual fluid (notably in the SRF compartment) that had improved from baseline and subsequently stabilized was not detrimental to VA in patients with nAMD and PCV; however, further investigation may be warranted to fully elucidate the threshold for tolerating persistent SRF in patients with PCV. Therefore, in contrast to the traditional T&E retreatment criteria (which require complete resolution of fluid on OCT to extend the treatment interval), some residual SRF, not IRF, may be tolerated without compromising visual outcomes when extending treatment intervals.^{18,20,23,79} This strategy would allow more patients, especially those who have minimal, persistent SRF despite continuous injections, to safely extend treatment intervals. Preliminary data indicate that SRF may reduce the risk of macular atrophy, which is hypothesized to be due to the potential of SRF to act as a buffer that protects photoreceptors from any potential toxicity that may arise from direct contact with the diseased RPE.⁸⁰ The consensus recommendations also highlight that importance of differentiating between exudative and degenerative IRF based on retinal morphology,⁶² especially when IRF persists despite multiple high-frequency dosing, as patients with exudative IRF are usually more responsive to anti-VEGF therapy versus those with degenerative IRF.⁸¹

Although T&E regimens have been assessed in many studies with aflibercept, ranibizumab, and bevacizumab, limited head-to-head RCTs are comparing the efficacy of available anti-VEGF agents with T&E regimens (Supplementary Digital Content, Table 2, <http://links.lww.com/APJO/A114>), and there is currently limited evidence on the use of T&E with conbercept or brolicizumab. However, a network meta-analysis and indirect comparison by Ohji et al⁴⁸ determined that patients receiving aflibercept T&E achieved and maintained vision gains with approximately 6 fewer injections over 2 years compared with ranibizumab T&E. Given the longer half-life of aflibercept compared with other currently available anti-VEGF agents, aflibercept seems well suited to maximizing the benefits of a T&E regimen in patients with nAMD and PCV.

The coronavirus (COVID-19) pandemic has further emphasized the importance of patient adherence and persistence with regard to treating retinal disorders.^{82–85} Patients with retinal disorders being treated at monthly or nearly monthly intervals might be more likely to miss an appointment than patients who have extended treatment intervals, which may lead to a higher risk of irreversible vision loss. As evidence suggests, and on the recommendation of some ophthalmic societies,⁸⁶ appropriate implementation of T&E regimens with interval extension based on predefined criteria, such as those that allow tolerance of persistent minimal SRF in the absence of IRF, may reduce the need for nonessential clinic visits and person-to-person contact in the COVID-19 setting without compromising vision. Similarly, drug safety is even more important now. Extensive data from clinical trials on the use of aflibercept, ranibizumab, and off-label bevacizumab have established the safety profile of

intravitreal anti-VEGF agents, including their use with T&E regimens.^{20,27,87,88} Conversely, a safety signal was confirmed with brolicizumab for adverse events that may result in severe vision loss termed as “retinal vasculitis” and/or “retinal vascular occlusion”, typically occurring in the presence of intraocular inflammation and requiring extensive imaging, patient monitoring, and increased time spent in the clinic.⁸⁹ This warrants careful consideration by clinicians, particularly in the COVID-19 setting where unnecessary clinic visits should be kept to a minimum.⁹⁰

Verteporfin PDT can be used as an adjunctive treatment for PCV eyes. Results from the EVEREST II study demonstrated that a combination of ranibizumab and PDT was superior to ranibizumab monotherapy,^{11,12} while the PLANET study demonstrated that aflibercept monotherapy was non-inferior to aflibercept plus rescue PDT.^{7,13} However, to date, there has been no strong evidence suggesting the role of PDT as part of a T&E regimen in nAMD or PCV patients.

Although this publication aimed to review the literature on use of T&E for the management of nAMD and PCV in the Asia-Pacific region, it was noted that a large proportion of studies identified by the systematic search were not performed in this region. In addition to other current guidelines on the T&E regimen for nAMD,^{4,5,91,92} this consensus recommendation has incorporated the latest evidence which allows more flexible interval adjustment by 2 to 4 weeks with an extension up to 16 weeks when using aflibercept; includes fluid compartment consideration when determining retreatment intervals, and also includes the recent evidence of T&E regimens in PCV.

Further studies are required to compare the long-term efficacy of T&E regimens with other treatment regimens, across all available anti-VEGF agents in nAMD/PCV, and in other nAMD subtypes, such as retinal angiomatous proliferation. The implementation of T&E regimens with novel therapies in the pipeline, such as novel therapeutic molecules, port delivery systems, gene therapy, as well as the potential role of artificial intelligence in nAMD and PCV management, are also warranted.

Finally, there is currently insufficient evidence in the literature regarding stopping anti-VEGF treatment for nAMD and PCV. Careful patient selection is recommended should clinicians decide to discontinue treatment after a sustained treatment period at consecutive 16-week intervals; such patients should be carefully counseled and monitored with access to retreatment should visual symptoms be apparent.

CONCLUSIONS

Implementation of anti-VEGF T&E regimens could potentially provide meaningful visual outcomes and minimize the burden of frequent clinic visits for patients with nAMD and PCV in the Asia-Pacific region. Based on recent evidence, consensus recommendations for implementation of T&E allow gradual extension of treatment intervals by 2 to 4 weeks between visits up to a maximum interval of 16 weeks with aflibercept, and adjustment of treatment intervals by 2 weeks between visits up to a maximum interval of 12 weeks with ranibizumab or bevacizumab. Differentiation of fluid compartments during follow-up might allow clinicians to maintain or extend treatment intervals without compromising vision in patients with persistent residual SRF despite continuous treatment.

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