VISION ACADEMY

people | research | education

Treatment regimens for optimizing outcomes in patients with neovascular age-related macular degeneration

The Vision Academy is supported by Bayer. This presentation has been developed by Vision Academy members and does not necessarily reflect the views of Bayer.
October 2024 | MA-PFM-OPHT-ALL-1334-1

BAYER

The Vision Academy is a group of over 80 international experts who, through their collective expertise, provide consensus guidance for managing clinically challenging situations, especially in areas of controversy or with insufficient conclusive evidence.

The Vision Academy is funded and facilitated by Bayer.

This presentation has been developed by Vision Academy members and is intended for healthcare professionals. The opinions expressed, and guidance laid out, by the Vision Academy are developed independently by the members and do not necessarily reflect the opinions of Bayer.

Contents

Click on a section

VISION ACADEMY

BACK TO CONTENTS

Objectives

To discuss the principles of an ideal treatment regimen for nAMD	To update previous Vision Academy recommendations on the fundamental principles of anti-VEGF treatment regimens	Develop an evidence-based treatment algorithm for use in clinical practice

?

QUESTION

How can we refine current practice for the treatment of nAMD?

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

VISION ACADEMY

BACK TO CONTENTS

VISION ACADEMY

people | research | education

Background

Treatment of nAMD with VEGF inhibitor therapy

- Treatment of nAMD has advanced in the past decade, with key trials demonstrating the efficacy of VEGF inhibitor therapy in this indication[1-3]
- Outcomes in clinical settings are often inferior to those reported in clinical trials,[4,5] likely due to:[6-8]
  - Undertreatment
  - Poor adherence
  - Inappropriate treatment decisions
- Guidance on treatment has been previously proposed, but with ongoing changes in the treatment landscape, it is timely to consider a set of **current, pragmatic, clinically applicable guidelines** that can close the gap between clinical trial and real-world outcomes

?

CHALLENGE REQUIRING VISION ACADEMY GUIDANCE

How can we utilize the knowledge from both clinical trials and real-world evidence to update previous recommendations and create a usable treatment framework?

RECOMMENDATION

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

1. Rosenfeld PJ *et al. N Engl J Med* 2006; 355 (14): 1419–1431; 2. Kodjikian L *et al*. *Ophthalmology* 2013; 120 (11): 2300–2309; 3. Dugel PU *et al*. *Ophthalmology* 2020; 127 (1): 72–84; 4. Kang HM *et al*. *Am J Ophthalmol* 2013; 156 (4): 652–660; 5. Veritti D *et al. J Clin Med* 2022; 11 (2): 325; 6. Hykin P *et al. JAMA Ophthalmol* 2019; 137 (11): 1256–1264; 7. Holz FG *et al. Br J Ophthalmol* 2013; 97 (9): 1161–1167; 8. Rao P *et al*. *Ophthalmology* 2018; 125 (4): 522–528.

VISION ACADEMY

Early initiation of treatment with VEGF inhibitors

- Early initiation of VEGF inhibitor therapy has been found to maximize visual outcomes in patients with nAMD, and a prolonged delay between symptom onset and treatment initiation has been identified as a **strong predictor of poor visual outcomes**:[1]
  - Patients with a delay in treatment of >21 weeks compared to <7 weeks had a **2.6-fold increase in the risk of worsening vision** after treatment
- Studies of nAMD in fellow eyes show considerably better outcomes when treatment is commenced early, as the fellow eyes benefit from opportunistic monitoring during visits intended for the affected eye[2-4]
- Early, intensive treatment is associated with favorable outcomes, with a retrospective analysis from the UK demonstrating greater visual improvements in patients who underwent a **loading phase** at the start of treatment (the first three doses received within 90 days) versus those who did not undergo one[5]
- However, this early intervention is subject to patients presenting with early disease, which could **go undetected if their vision remains good**[6]

CHALLENGE REQUIRING VISION ACADEMY GUIDANCE

Given the importance of early treatment initiation, it is crucial to establish a practical framework for clinical practice to ensure optimal patient outcomes

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

1. Lim JH *et al*. *Am J Ophthalmol* 2012; 153 (4): 678–686.e1–2; 2. Zarranz-Ventura J *et al. Ophthalmology* 2014; 121 (10): 1966–1975; 3. Bek T, Klug SE. *Grafes Arch Clin Exp Ophthalmol* 2018; 256 (11): 2061–2068; 4. Lövestam Adrian M *et al*. *Acta Ophthalmol* 2022; 100 (7): 776 –774; 5. Hykin P *et al. Clin Ophthalmol* 2016; 10: 87–96; 6. Nguyen V *et al. Clin Exp Ophthalmol* 2018; 46 (3): 266–274.

VISION ACADEMY

BACK TO CONTENTS

VISION ACADEMY

people | research | education

Clinical challenges

BACK TO CONTENTS

Clinical challenges requiring guidance

Effective treatment regimens

What new insights into nAMD treatment from clinical trials and real-world evidence could be incorporated into clinical practice?

Practical recommendations

How can we use this current evidence to update existing recommendations and establish a contemporary treatment framework?

Click on a section

nAMD, neovascular age-related macular degeneration.

VISION ACADEMY

BACK TO CONTENTS

VISION ACADEMY

people | research | education

Insights from clinical trials and real-world evidence

Variable treatment regimens for nAMD

- The high treatment burden of monthly treatments as per landmark trials is unsustainable in real-world practice
- Clinical trials have been conducted specifically to overcome this challenge by evaluating the efficacy of non-monthly or variable treatment regimens

Regimen	Outcome	Burden	Trial(s)
Quarterly dosing	Poor	Low	PIER,[1] EXCITE[2]
PRN	Good	High	CATT[3]
T&E	Good	Balanced	TREX,[4] TREND,[5] CANTREAT[6]

A systematic review of 62 PRN and 8 T&E studies found that the **T&E regimen had better outcomes** (10 letter gain with 8.1 injections) than the PRN regimen (5.4 letter gain with 5.6 injections)[7]

A recent meta-analysis also demonstrated **better outcomes with the T&E than the PRN approach in clinical trial and real-world settings**, as well as across different agent types[8]

nAMD, neovascular age-related macular degeneration; PRN, *pro re nata* (as needed); T&E, treat-and-extend.

1. Regillo CD *et al*. *Am J Ophthalmol* 2008; 145 (2): 239–248; 2. Schmidt-Erfurth U *et al*. *Ophthalmology* 2011; 118 (5): 831–839; 3. Martin DF *et al*. *N Engl J Med* 2011; 364 (20): 1897–1908; 4. Wykoff CC *et al*. *Ophthalmology* 2015; 122 (12): 2514–2522; 5. Silva R *et al*. *Ophthalmology* 2018; 125 (1): 57–65; 6. Kertes PJ *et al*. *JAMA Ophthalmol* 2020; 138 (3): 244–250; 7. Li E *et al*. *Cochrane Database Syst Rev* 2020; 5 (5): CD012208; 8. Veritti D *et al. J Clin Med* 2022; 11 (2): 325.

“Tailored” or “traditional” T&E regimens

Several clinical trials aimed to modify the “traditional” T&E regimen by allowing for intervals to be extended or maintained, depending on disease severity.

There are two notable differences between “tailored” and “traditional” T&E regimens:

Differentiation of SRF as a marker of reduced disease severity[1]

- Although any fluid (IRF or SRF) had been considered a sign of disease activity that required treatment intervals to be shortened, recent evidence from the **FLUID** and **ARIES** studies has shown that **stable SRF may be tolerated[2,3]**

Increased length of treatment intervals and the longest permissible interval[3,4]

The **ALTAIR** study looked at the following interval alterations:

- **Extended** if no fluid was detected
- **Maintained** if fluid was present but decreasing
- **Shortened** if fluid was persistent or unchanged

These varying treatment intervals and this stratification of disease severity meant that patients could be treated with a much more personalized regimen than with the traditional T&E regimen

IRF, intraretinal fluid; SRF, subretinal fluid; T&E, treat-and-extend.

1. Chaudhary V *et al*. *Retina* 2022; 42 (4): 589–606; 2. Arnold JJ *et al*. *BMC Ophthalmol* 2016; 16: 31; 3. Mitchell P *et al*. *Retina* 2021; 41 (9): 1911–1920; 4. Ohji M *et al*. *Adv Ther* 2020; 37 (3): 1173–1187.

New VEGF inhibitor agents

- The choice of agent often depends on physician preference, which, in turn, can depend on disease subtype and/or the financial status of the patient and prevailing healthcare reimbursement rules[1]
- An agent's durability of action can be another consideration in treatment selection[2]
  - This durability is a product of both the drug's half-life and drug clearance by the individual patient
  - If the half-life can be accurately determined, physicians may be able to administer agents suited to extended treatment intervals specific to individual patients

- In clinical trials, **brolucizumab** and **faricimab** have demonstrated the potential to support extended regular treatment intervals of 12 weeks and 16 weeks, respectively[3,4]
  - The **TENAYA** and **LUCERNE** trials established **non-inferiority** between **faricimab 6 mg administered at intervals of up to 16 weeks** and **aflibercept 2 mg administered every 8 weeks**
- Extended intervals of this length **may not be suitable for all patients** and would require **disease activity monitoring visits**, which may be difficult to implement in clinical practice[3,4]

VEGF, vascular endothelial growth factor.

1. Lee WK *et al*. *JAMA Ophthalmol* 2018; 136 (7): 786–793; 2. Veritti D *et al*. *Pharmaceutics* 2022; 14 (2): 265; 3. Dugel PU *et al*. *Ophthalmology* 2020; 127 (1): 72–84; 4. Heier JS *et al*. *Lancet* 2022; 399 (10326): 729–740.

Different formulations of anti-VEGF inhibitors

Different formulations of established drugs, such as **aflibercept 8 mg**, may also provide greater efficacy and/or durability than currently available options

- In the **Phase 2 CANDELA** trial, a greater proportion of eyes treated with aflibercept 8 mg versus 2 mg achieved a fluid-free center subfield at Week 16: 51% (n=27) versus 34% (n=18); treatment difference: 17.0 percentage points (95% CI: –1.6, 35.5); p=0.08[1]

- In the **follow-up Phase 3 PULSAR trial**, mean increases of 5.6 and 5.5 letters were observed at Week 96 in patients treated with aflibercept 8 mg at 12- and 16-week intervals, respectively, with **88% of patients reaching a last assigned dosing interval of ≥12 weeks, 71% reaching an interval of ≥16 weeks, and 47% reaching an interval of ≥20 weeks at the end of the 2-year study**
- The vision gains achieved with these extended intervals were similar to the 6.6-letter gain among patients treated with aflibercept 2 mg at 8-week intervals[2]

Although newer agents and different formulations show potential for increased efficacy and durability, and could change the treatment landscape of nAMD, **they should be used with caution and adverse events should be monitored closely**

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

1. Wykoff CC *et al*. *JAMA Ophthalmol* 2023; 141 (9): 834–842; 2. Lanzetta P *et al*. Intravitreal aflibercept 8 mg injection in patients with neovascular age-related macular degeneration: 60-week and 96-week results from the Phase 3 PULSAR trial. Presented at the European Society of Retina Specialists (EURETINA) Congress, Amsterdam, the Netherlands, October 5–8, 2023.

BACK TO CONTENTS

VISION ACADEMY

people | research | education

Vision Academy recommendations

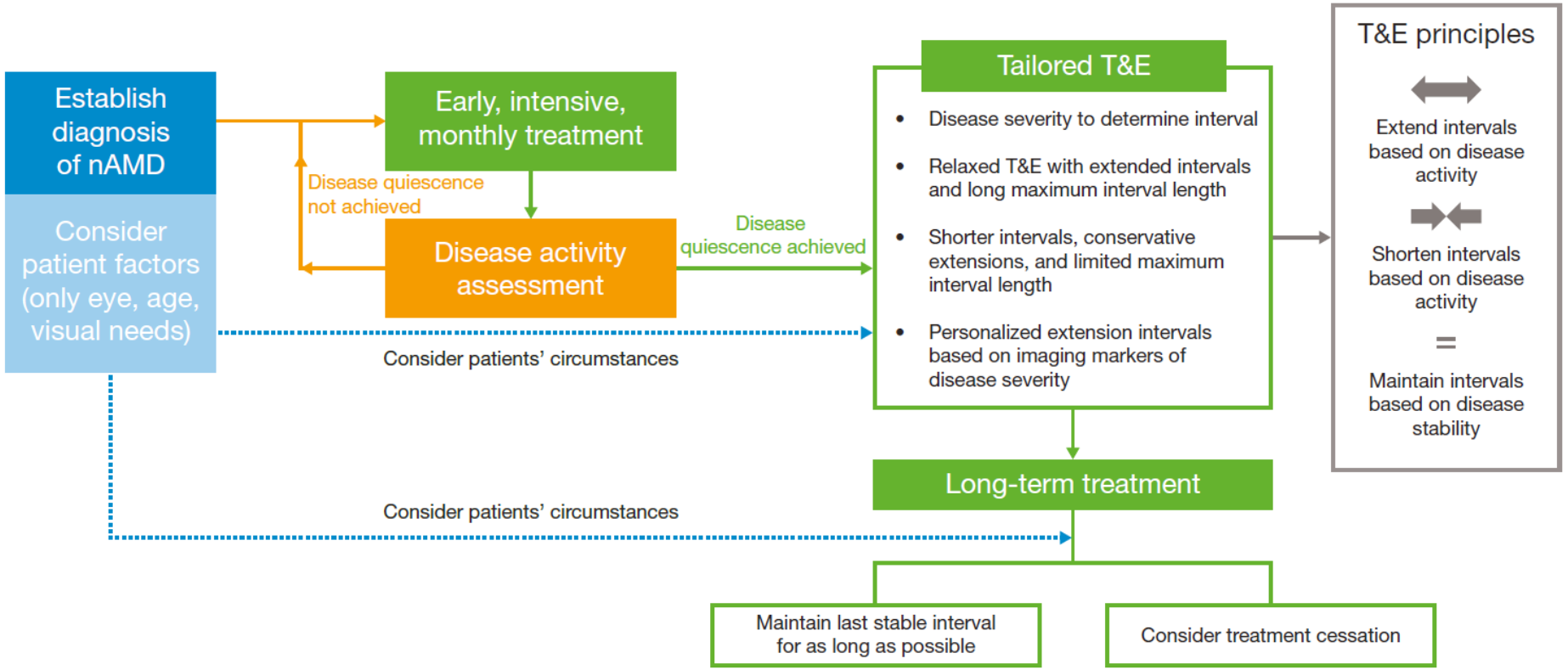
Intensive treatment should start early to maximize visual outcomes

- Treatment of nAMD should commence **when disease activity is detected**; however, this can be challenging, as patients may not be aware that their symptoms herald a more serious condition
- **Early, intensive treatment** should be considered to achieve disease quiescence rapidly and maximize long-term visual outcomes

nAMD, neovascular age-related macular degeneration.

Recommended algorithm for the treatment of nAMD

The following algorithm, endorsed by the Vision Academy, includes the **"tailored"** approach to T&E regimens



nAMD, neovascular age-related macular degeneration; T&E, treat-and-extend.

A T&E regimen should start after lesion quiescence is achieved

- Currently, T&E has been shown to be the **most balanced treatment strategy**, given its good visual outcomes and low treatment burden[1-3]
- Globally, many physicians pivot to T&E regimens to **mitigate a high treatment burden**[4]
- In some cases, nAMD lesions are aggressive and **disease quiescence cannot be achieved despite regular and frequent treatments** over an extended period[5-7]
  - These eyes fall broadly into the category of **refractory / treatment-resistant nAMD**
- Strategies that have been shown to be effective in these eyes include **switching anti-VEGF agents** or **increasing the dose**[8]
  - Evidence for other strategies, such as increasing dosing frequency, is limited[9]

nAMD, neovascular age-related macular degeneration; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

1. Veritti D *et al. J Clin Med* 2022; 11 (2): 325; 2. Abdin AD *et al*. *Graefes Arch Clin Exp Ophthalmol* 2019; 257 (5): 1671–1677; 3. Wykoff CC *et al*. *Br J Ophthalmol* 2018; 102 (4): 460–464; 4. Singh RP, Stone TW, Hahn P, eds. 2019 Global Trends in Retina Survey. Chicago, IL: American Society of Retina Specialists; 2019; 5. Kumar N *et al*. Retina 2013; 33 (8): 1605–1612; 6. Schachat AP. *Am J Ophthalmol* 2013; 156 (1): 1–2.e1; 7. Chang AA *et al*. *Ophthalmology* 2014; 121 (1): 188–192; 8. Brown DM *et al*. *Ophthalmology* 2013; 120 (2): 349–354; 9. Mimouni M *et al*. *Jpn J Ophthalmol* 2018; 62 (6): 652–658.

Treatment intervals can be tailored according to disease severity

- When starting a T&E regimen after initial disease quiescence, treatment intervals can be tailored according to disease severity rather than the presence of disease activity
- Disease severity can be contingent on fluid type and nature of disease, and may incorporate newer computational imaging techniques
- Despite good outcomes in patients treated with longer intervals and tolerance of some disease activity, more intensive treatment may be considered for patients treated for nAMD in their only-seeing eye
- Real-world evidence is key to making informed decisions about long-term treatment and cessation, as it is costly and impractical to continue randomized controlled trials over several years[1]
  - Long-term results from real-world studies have shown that most eyes are able to maintain vision gains on a T&E regimen after 2 years

nAMD, neovascular age-related macular degeneration; T&E, treat-and-extend.

1. Rayess N *et al*. *Am J Ophthalmol* 2015; 159 (1): 3–8.e1.

Long-term treatment should be continued, but suspension can be considered

- Treatment should be continued for as long as the patient can tolerate it
  - Long treatment intervals can be considered in quiescent disease states to enable background control of the disease
- Treatment suspension with good vision can be attempted in consultation with the patient, but close follow-up with OCT monitoring should be performed to ensure timely treatment if the disease reactivates[1]
  - Treatment suspension should be strongly considered when further treatment is futile and/or when no further gains in vision are possible
- The status of the fellow eye is also important when considering treatment suspension
  - Caution should be exercised when considering treatment suspension in cases where the better-seeing eye is undergoing treatment, and the other eye is lost to end-stage nAMD

nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography.

1. Wong DT *et al*. *Retina* 2020; 40 (6): 1010–1020.

BACK TO CONTENTS

VISION ACADEMY

people | research | education

Summary

Vision Academy recommendations

- Intensive treatment should start early to maximize visual outcomes
- A T&E regimen should start after lesion quiescence is achieved
- Treatment intervals can be tailored according to disease severity
- Long-term treatment should be continued, but suspension can be considered

T&E, treat-and-extend.

Initiating T&E in a clinical setting

- T&E regimens consist of two main components, which can be performed in a **single visit (one-stop)** or **separate visits (two-stop):**[1]
  - Assessment of disease severity, which results in a decision on treatment interval length
  - Administration of treatment
  - One-stop delivery is preferred; however, it results in longer visit times and puts greater strains on clinical resources
  - Two-stop delivery results in shorter visit times but requires patients to attend more visits

- Bilateral same-day treatment can reduce the treatment burden but may harm long-term vision in the second eye if treatment intervals are extended[2]
- Eyes should be treated individually, prioritizing the shorter interval
- The COVID-19 pandemic has made virtual clinics more acceptable for monitoring nAMD in T&E regimens, allowing same-day assessments and treatment, with decisions for the next interval provided asynchronously by the physician at a later time[3]

nAMD, neovascular age-related macular degeneration; T&E, treat-and-extend.

1. Juncal VR *et al*. *Ophthalmologica* 2019; 242 (1): 1–7; 2. Cornish EE *et al*. *Retina* 2021; 41 (1): 118–124; 3. Gilbert AW *et al*. *BMJ Open Qual* 2020; 9 (2): e000985.

Further considerations

- Some recommendations endorsed by the Vision Academy serve to affirm current practices, while others offer new insights that may change practice patterns

- The departure from considering disease activity as binary, and accepting the concept of disease severity, can result in more personalized treatment intervals

- Disease severity can be measured as various aspects, including the quantification of fluid, fluid in different retina compartments, and even the location of fluid
  - This has become apparent with trials like PULSAR,[1] which tolerated non-foveal fluid as part of the retreatment criteria

- With new treatments on the horizon, the treatment landscape of nAMD will continue to evolve, and the continued use of both clinical trial and real-world evidence will become even more important to ensure that the most effective treatments are chosen for clinical practice

nAMD, neovascular age-related macular degeneration.

1. Lanzetta P *et al*. Intravitreal aflibercept 8 mg injection in patients with neovascular age-related macular degeneration: 60-week and 96-week results from the Phase 3 PULSAR trial. Presented at the European Society of Retina Specialists (EURETINA) Congress, Amsterdam, the Netherlands, October 5–8, 2023.

VISION ACADEMY