Discussion and debate:

Optimal treatment regimen with anti-VEGF

Reactive: Mr James Talks
Proactive: Professor Francesco Bandello

Presentation of viewpoint: Professor Paolo Lanzetta

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Session aims

➢ To debate and discuss evidence for a ‘reactive’ versus a ‘proactive’ anti-VEGF therapeutic regimen

➢ To provide a summary of the Vision Academy’s Viewpoint on the optimal treatment regimen with anti-VEGF
  • The Viewpoint can be found in your symposium pack

VEGF, vascular endothelial growth factor.
Is there a case for a reactive anti-VEGF therapeutic regimen?

Mr James Talks
Royal Victoria Infirmary,
Newcastle Upon Tyne, UK
## Financial and other disclosures

I have the following financial interests or relationships to disclose

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C, consultant; L, lecture fees; S, grant support
Why consider reactive treatment?

- There are several safety concerns associated with over-treating:
  - The risk of post-injection endophthalmitis is small but real
  - Occurrences of RPE / photoreceptor atrophy have been observed following ranibizumab and bevacizumab injections\(^1,2\)
  - A significant temporary decrease in cone function has been observed in patients receiving bevacizumab injections\(^3\)

- Reactive or PRN treatment regimens aim to alleviate the burden on patients, the physician, and the system, as well as the financial costs associated with more frequent IVT injections

IVT, intravitreal; PRN, pro re nata (as needed); RPE, retinal pigment epithelium.

The most frequent adverse event associated with IVT injections is endophthalmitis

- Endophthalmitis rates after IVT injections are low (~1 in 2000), but this is compounded by repeated treatment
  - The incidence of endophthalmitis may be as high as 1% when viewed over a 2-year course of treatment

IVT, intravitreal.
Intense IVT injection regimens severely affect quality of life

In a European survey of 131 retinal patients:

- 93% reported anxiety relating to their most recent injection
- 47% reported adverse physical effects, such as exhaustion, which was related either to the injection itself or to anxiety about the injection
- 54% reporting anxiety ≥2 days prior
- 42% desired fewer injections to achieve the same visual results

Reactive dosing regimens enable a reduction in the number of injections that patients receive

- In a 12-month, phase III, open-label study of ranibizumab in patients with nAMD, patients were treated with a reactive injection schedule after three initial monthly injections:
  - Patients received 70% fewer injections versus fixed monthly dosing, with 80% of the treatment effect.
  - In the 9-month study period after loading, 20% of patients did not require any additional injections.

In a meta-analysis of 2-year head-to-head studies, reactive dosing enabled fewer injections:

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean difference, IV (95% CI)</th>
<th>Favors reactive</th>
<th>Favors monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATT 2012</td>
<td>-9.50 (-10.22, -8.78)</td>
<td></td>
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<tr>
<td>HARBOR 2014</td>
<td>-7.20 (-7.94, -6.46)</td>
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<tr>
<td>Total</td>
<td>-8.39 (-8.90, -7.87)</td>
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CATT, Comparison of Age-Related Macular Degeneration Treatments Trials; CI, confidence interval; IV, independent variable; nAMD, neovascular age-related macular degeneration.

Reactive dosing regimens can provide similar efficacy to fixed monthly injections

The CATT non-inferiority study compared different dosing regimens of bevacizumab and ranibizumab in patients with nAMD\textsuperscript{1}

- VA outcomes were similar between reactive and fixed dosing regimens


\begin{tabular}{|c|c|c|c|}
\hline
Follow-up (weeks) & Mean change in VA score from baseline (no. of letters) & 0 & 4 & 12 & 24 & 36 & 52 & 64 & 76 & 88 & 104 \\
\hline
\hline
Ranibizumab reactive & 8.8 & \textbf{7.8} & 7.4 & 7.1 & 6.8 & 6.5 & 6.2 & 5.9 & 5.6 & 5.3 & 5.0 \\
Ranibizumab monthly & 8.8 & \textbf{7.8} & 7.4 & 7.1 & 6.8 & 6.5 & 6.2 & 5.9 & 5.6 & 5.3 & 5.0 \\
Bevacizumab reactive & 8.8 & \textbf{7.8} & 7.4 & 7.1 & 6.8 & 6.5 & 6.2 & 5.9 & 5.6 & 5.3 & 5.0 \\
Bevacizumab monthly & 8.8 & \textbf{7.8} & 7.4 & 7.1 & 6.8 & 6.5 & 6.2 & 5.9 & 5.6 & 5.3 & 5.0 \\
\hline
\end{tabular}

\textit{p}=0.046, fixed monthly vs. reactive, at 104 weeks
The efficacy of reactive and T&E regimens are not largely dissimilar

- Retrospective comparisons of reactive and T&E regimens are inconclusive:
  - In nAMD, no strong differences in anatomical and functional improvements were observed\(^1\)
  - Poor performance of reactive regimens in real-world studies has been attributed to a low mean number of injections and less-than-monthly visits; both common to T&E\(^2\)

nAMD, neovascular age-related macular degeneration; T&E, treat-and-extend; VA, visual acuity.
2013: 89-year-old female

Left eye

- July 2013: 0.6 (55)
- Feb 2018 after 3 injections: 0.3 (70)

Right eye

- July 2016: 0.3 (70)
- Feb 2018 after 5 injections: 0.3 (70)

Now aged 93 years: 4.5 years since first treatment, vision maintained with 3 injections in left eye and 5 in right eye
Summary

- Potential VA improvements must be balanced against the burden and complications of frequent IVT injections.
- Reactive treatment regimens aim to reduce injection frequency without compromising VA outcomes.
- Careful monitoring is crucial to prevent deterioration.
  - Maintenance of all monitoring sessions is essential.

IVT, intravitreal; VA, visual acuity.
Optimal treatment regimen with anti-VEGF in AMD: Proactive

Francesco Bandello, MD, FEBO
Professor and Chair, Department of Ophthalmology, University Vita-Salute, Scientific Institute San Raffaele, Milan, Italy

AMD, age-related macular degeneration; VEGF, vascular endothelial growth factor.
Financial and other disclosures

I have the following financial interests or relationships to disclose:

- Alcon
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- Hoffmann-La Roche
- Carl Zeiss Meditec
- Novartis Pharmaceuticals Corporation
- NTC Pharma
- Sifi
- Sooft
- ThromboGenics

Advisory board member
### Anti-VEGF treatment regimens in AMD

<table>
<thead>
<tr>
<th>PROACTIVE</th>
<th>REACTIVE</th>
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<tr>
<td>➢ Fixed dosing</td>
<td></td>
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<tr>
<td>– Monthly(^1)-(^3) or quarterly(^4)</td>
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<tr>
<td>➢ Treat-and-extend</td>
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<tr>
<td><strong>Pro re nata (PRN):</strong></td>
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<tr>
<td>– Monthly visits(^3),(^5)-(^6)</td>
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<td>– Extended visits(^7)-(^8)</td>
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<tr>
<td>– Treat-to-target</td>
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AMD, age-related macular degeneration; VEGF, vascular endothelial growth factor.

Optimal ≠ perfect
MARINA and ANCHOR trials using fixed dosing regimens: gold standard of treating nAMD

ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration; PDT, photodynamic therapy; SE, standard error.

VIEW: fixed dosing with aflibercept q8 achieved optimal results

- Aflibercept monotherapy improved visual acuity in the overall wet AMD population

Combined VIEW 1 and VIEW 2 study data

Difference in LS mean at Week 52
- 9.3 2q4 (n=559)
- 8.7 Rq4 (n=538)
- 8.4 2q8 (n=535)
- 8.3 0.5q4 (n=538)

Difference in LS mean at Week 96
- 7.9 Rq4 (n=595)
- 7.6 2q8 (n=607)
- 7.6 2q4 (n=613)
- 6.6 0.5q4 (n=597)

0.5q4, aflibercept 0.5 mg every 4 weeks; 2q4, aflibercept 2 mg every 4 weeks; 2q8, aflibercept 2 mg every 8 weeks; AMD, age-related macular degeneration; BCVA, best corrected visual acuity; LOCF, last observation carried forward; LS, least square; Rq4, ranibizumab 0.5 mg every 4 weeks.

**PRN re-treatment criteria:**

**ALL REQUIRED MONTHLY MONITORING!**

**PRONTO (n=40)**
- Evidence of fluid in the macula
- >100 μm increase in CRT
- New macular hemorrhage or new leakage on FA
- Persistent fluid on OCT, 1 month after previous injection
- Re-treatment criteria in Year 2 amended to include any qualitative increase in the amount of fluid detected via OCT
- Mean change from baseline in BCVA at 12 months: +9.3 letters

**SAILOR cohort I (n=2378)**
- A 100 μm increase in CRT from the thinnest measurement recorded at any prior scheduled study visit
- Decreased VA >5 letters compared with any prior scheduled study visit
- Mean change from baseline in BCVA at 12 months: +2.3 letters

**SUSTAIN (n=513)**
- Either >5 letters VA loss or >100 μm increase in CRT
- Option not to treat if VA ≥79 letters or CRT ≤225 μm or change by <50 μm in CRT and <5 letters in BCVA after three consecutive treatments
- Mean change from baseline in BCVA at 12 months: +3.6 letters

**MONT BLANC (n=255)**
- A 100 μm increase in CRT from the thinnest measurement recorded at any prior scheduled study visit
- Evidence of subretinal fluid
- New subretinal hemorrhage
- Decreased VA >5 letters compared with VA score from the previous scheduled study visit
- Mean change from baseline in BCVA at 12 months: +4.4 letters

BCVA, best corrected visual acuity; CRT, central retinal thickness; FA, fluorescein angiography; OCT, optical coherence tomography; PRN, pro re nata (as needed); VA, visual acuity.
Modest VA improvements over 12 months with mean of 5.6 injections in SUSTAIN

Mean change in the VA of study eye over time in the SUSTAIN safety study

BCVA, best corrected visual acuity; SE, standard error; VA, visual acuity.
The simple fact is: visual outcomes correlate with number of injections

Better outcomes were observed with fixed dosing schedules after three initial monthly doses.

VA gains of >7 letters were maintained during T&E phase on aflibercept

- Retrospective study to assess real-life outcomes with aflibercept for the treatment of treatment-naïve neovascular AMD (n=85) in routine clinical practice in Sweden

- BCVA improved significantly in the first year when patients were treated as per the bimonthly licensed posology, and the improvement was sustained for 6 months after switching to a T&E regimen

![Mean BCVA change from baseline to Month 18](image)

- By Month 12: +7.2 letters (7.7 injections)
- By Month 18: +8.7 letters (9.9 injections)

Approximately two injections were administered in the final 6 months of the study while maintaining the 12-month VA gain of 7.2 letters

AMD, age-related macular degeneration; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; LOCF, last observation carried forward; T&E, treat-and-extend; VA, visual acuity.

Real-world evidence: PRN limitation due to insufficient visits and injections compared to T&E

Meta-analysis of ~26,360 patients from 42 real-world observational studies, published between 2007 and 2015, reporting outcomes of intravitreal ranibizumab for nAMD. Random-effects estimate given.

ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration; PRN, pro re nata (as needed); T&E, treat-and-extend; VA, visual acuity.

However, that does not mean that **ALL** patients require proactive treatment

I prefer T&E in the following situations:

- Aggressive disease needing proactive rather than reactive treatment (e.g., RAP, CNV due to angioid streaks, vascularized PED, large classic CNV)
- Only-eye patients
- Inability to monitor disease frequently (4–6 weekly intervals) and indefinitely (e.g., co-morbidities, foreigners)
- Early recurrent disease: return of disease activity during Months 3–5 is critical

CNV, choroidal neovascularization; PED, pigment epithelial detachment; RAP, retinal angiomatous proliferation; T&E, treat-and-extend.
Optimal treatment regimen with anti-VEGF in AMD: proactive
What is the Vision Academy’s position?

Professor Paolo Lanzetta

University of Udine, Italy
The fundamental principles of an anti-VEGF treatment regimen

The Vision Academy has identified four principles that are fundamental to any treatment regimen for anti-VEGF management of retinal diseases:

1. Maximize and maintain VA benefits for all patients
2. Decide when to treat next, rather than whether to treat now
3. Titrate the treatment intervals to match patients’ needs
4. Treat at each monitoring visit

VA, visual acuity; VEGF, vascular endothelial growth factor.
The fundamental principles of an anti-VEGF treatment regimen

1. Maximize and maintain VA benefits for all patients

- This principle should be the aim for all patients undergoing anti-VEGF treatment
- The impact on a patient’s quality of life of improving and maintaining VA gains should not be underestimated
  - A five-letter gain in VA has been shown to nearly double a patient’s ability to read a newspaper, and it increases their ability to drive at night or in difficult conditions
- Early initiation of therapy and a sufficient frequency of injections are both essential for maximizing and maintaining gains in VA

VA, visual acuity.

The fundamental principles of an anti-VEGF treatment regimen

2. Decide when to treat next, rather than whether to treat now

- A proactive approach, where therapy is administered to minimize the risk of disease recurrence, may be necessary in order to stay ahead of the disease
  - At each clinic visit, the physician administers treatment and decides when to administer the next injection*

*Based on current VA and anatomic status.
PRN, pro re nata (as needed); T&E, treat-and-extend; VA, visual acuity.

Improves patient experience
- Predictable timing of the next injection
- Knowledge that an injection will be administered at every visit

Improves clinic flow
- Advance planning gives physicians more time to submit the necessary paperwork in health systems where approval is required prior to the next injection

Current and emerging data suggest that better VA outcomes can be achieved with T&E versus PRN¹,²

The fundamental principles of an anti-VEGF treatment regimen

3. Titrate the treatment intervals to match patients’ needs
   - The duration of VEGF suppression varies between patients and differs between anti-VEGF agents\(^1\)–\(^3\)
   - Treatment should be personalized to the patient’s individual needs, with consideration of the VEGF suppression time of the agent used

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

The fundamental principles of an anti-VEGF treatment regimen

4. Treat at each monitoring visit

- Elimination of any delay between patient assessment and treatment minimizes the risk of unidentified disease recurrence
- A reduction in the number of appointments per patient will also have a positive impact on clinic flow
  - Scheduling one appointment for both monitoring and treatment should:

  Make it easier for patients to manage travel to and from the clinic; this is particularly important for those who have to travel long distances or who require assistance

Help ease some of the burden on the clinic and thus improve clinic flow

Help alleviate patients’ fear of disease recurrence through the adoption of a proactive approach and the knowledge that treatment will not be delayed

Summary

- The fundamental principles identified were:
  1. Maximize and maintain visual acuity benefits for all patients
  2. Decide when to treat next, rather than whether to treat now
  3. Titrate the treatment intervals to match patients’ needs
  4. Treat at each monitoring visit

- These principles support the adoption of a predictable, proactive, and manageable treatment regimen with consideration of individual patient needs and minimization of delays in treatment

- A treat-and-extend approach, as outlined by these principles, is supported by the Vision Academy as the treatment regimen of choice in retinal disease
Further reading

The Viewpoint ‘Fundamental principles of an anti-VEGF treatment regimen’ can be downloaded from:

www.visionacademy.org