Tavola rotonda: *Terapie intravitreali: update e innovazione*

Opzioni di regimi di trattamento: strategie a confronto

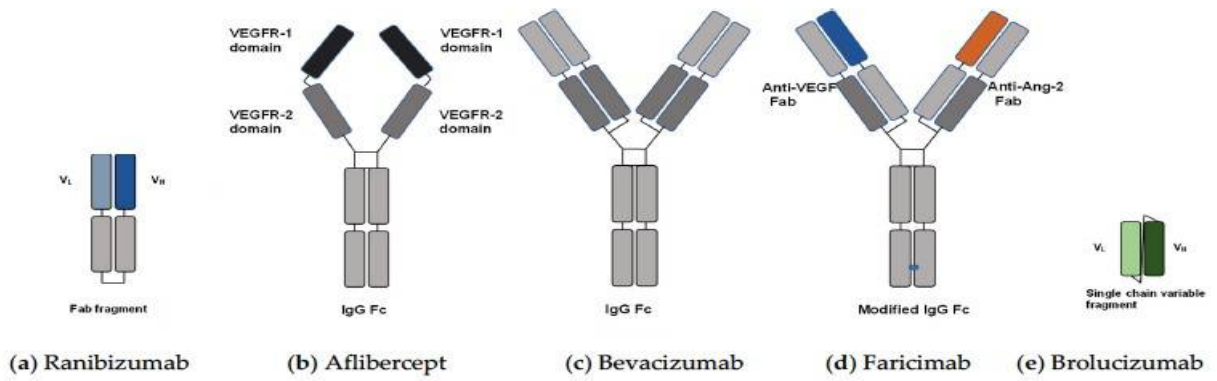
Maria Vadalà

Disclosures:
Consulente per Abbvie Italia SpA, Bayer Italia SpA, Novartis Italia SpA, Roche Italia SpA

Dipartimento di Biomedicina, Neuroscienze e Diagnostica avanzata
Sezione di Oftalmologia
Direttore: Prof. VME Bonfiglio

Le molecole anti-angiogeniche

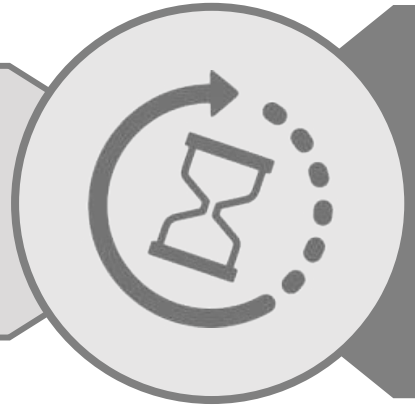
Drug	Unlicensed bevacizumab	Ranibizumab	Aflibercept	Brolucizumab	Faricimab
Format	Full antibody (IgG1)	Fab fragment	VEGFR1/2-Fc fusion protein	Single chain humanized antibody fragment	Full antibody (IgG1) Humanized, bispecific
Molecular weight	≈149 kDa	≈48 kDa	97-115 kDA	26 kDa	150 kDa
Clinical dose	1.25 mg	0.50 mg	2.00 mg / 8.00 mg	6.00 mg	6.00 mg
Emivita (giorni)	4.32-6.61	2.75-2.9	3.92-4.58	2.4-2.7	4.29



(a) Ranibizumab (b) Aflibercept (c) Bevacizumab (d) Faricimab (e) Brolucizumab

Il trattamento della wet-AMD nella pratica clinica prevede differenti regimi

Reattivo
(PRN,Wait and Extend)



- Visite di monitoraggio regolari e iniezioni solo in presenza di attività della patologia

Proattivo
(schema fisso T&E)

- Iniezioni ad ogni visita programmata, indipendentemente dall'attività della patologia
- Gli intervalli di trattamento vengono aggiustati in base alle risposte funzionali e/o morfologiche

- *García-Layana A et al. Drugs Aging 2015; 32 (10): 797–807.*
- *Mantel I. Transl Vis Sci Technol 2015; 4 (3): 6.*
- *Avitabile T. et al. Eur J Ophthalmol 2020;30(4):795-804*

I differenti regimi sono guidati dalla EBM e richiedono sforzi differenti

PRN= pro re nata,
Alias "treat and observe"

PRN
Best case: numero di iniezioni variabile + almeno10 visite/anno:
Worst case:
12 iniezioni +10 visite

- **Efficacia documentata con stretto monitoraggio**
- **Trattamento personalizzato**

- **Necessità di monitoraggi regolari mensili**
- **Difficilmente replicabile nella pratica clinica**
- **Possibile sottotrattamento**
- **Compliance**
- **Affollamento della struttura**

Avitabile T. et al. Eur J Ophthalmol 2020;30(4):795-804

Regime fisso mensile

Regime mensile fisso
12 iniezioni e
2-3 visite (?)

- Stretto controllo della malattia
- Numero ridotto di visite
- Risultati documentati

- Elevato numero di iniezioni
- Possibile sovratrattamento
- Potenziale maggiore rischio di eventi avversi
- Aspetti economici

Avitabile T. et al. Eur J Ophthalmol 2020;30(4):795-804

Regime fisso bimensile

Regime fisso bimensile
7 iniezioni con 2-3 visite (?)

- Numero ridotto di visite e iniezioni
- Risultati documentati
- Programmazione

- Controllo della malattia non personalizzato, rischio di sovratrattamento

Avitabile T. et al. Eur J Ophthalmol 2020;30(4):795-804

Treat and Extend

T&E
Best case:
6 iniezioni + 4 visite:
Worst case:
7 iniezioni + 5 visite

- Efficacia documentata
- Personalizzato e compliante
- Ridotto numero di visite e iniezioni
- Minori potenziali rischi di eventi avversi
- One stop

- Necessità di organizzazione

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Il «treat-and-extend» richiede …una organizzazione «ONE STOP»

Ad ogni visita per iniezione, si decide

SE ESTENDERE O RIDURRE

il successivo intervallo di trattamento, a seconda delle caratteristiche del paziente

Lanzetta P, Loewenstein A; Vision Academy Steering Committee. Fundamental principles of an anti-VEGF treatment regimen: optimal application of intravitreal anti-vascular endothelial growth factor therapy of macular diseases. *Graefes Arch Clin Exp Ophthalmol*. 2017;255(7):1259–1273.

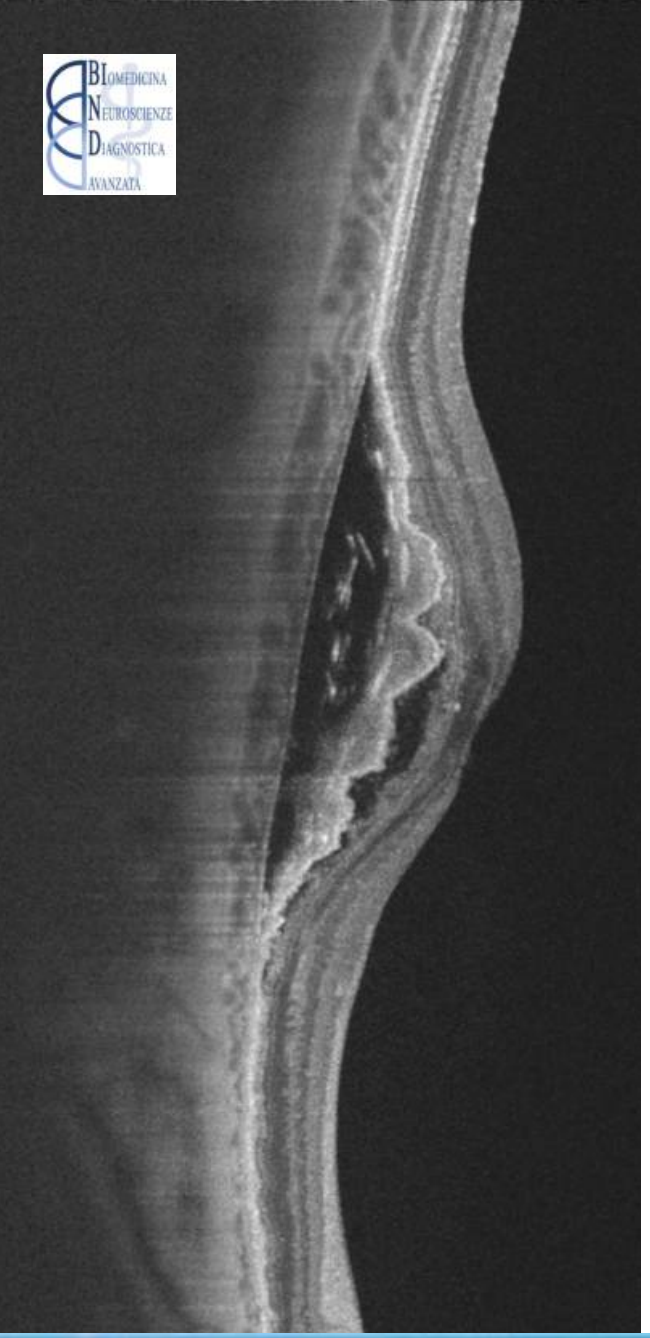
OBSERVE AND PLAN

O&P

Best case:
6 iniezioni+
3 visite:
Worst case:
9 iniezioni +
5 visite

- Efficacia relativamente documentata
- Personalizzato
- One stop

- Necessità di organizzazione
- Alto/medio numero di visite e iniezioni



La fase di induzione

- Variabile secondo scheda tecnica specifica: per la wAMD è omologata nel numero di 3 IV ogni 4 settimane *
- Variante oltre 3 IV: una iniezione al mese fino a che è ottenuta la massima acuità visiva e/o non ci sono segni di attività della patologia **

La fase di mantenimento

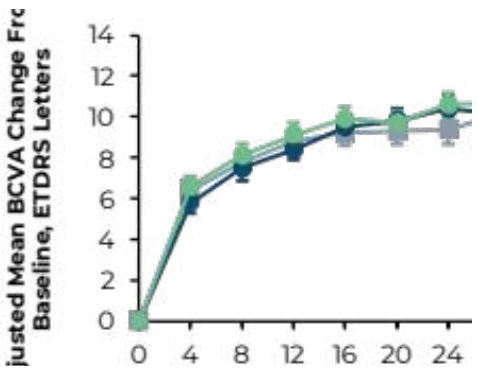
- definisce il regime di trattamento

* Eccetto per Brolucizumab in regime qw6
** Eccetto per Brolucizumab e Aflibercept 8mg

Altri regimi di trattamento

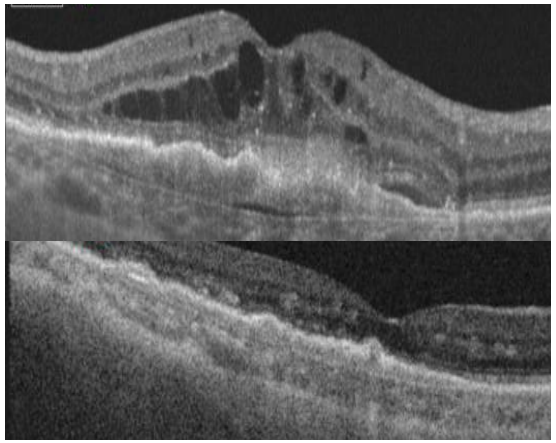
"Quarterly capped PR"
[Lala C, et al. Acta Ophthalmol. 2013;91:526–30],
"FUSION"
[Mones J, et al. Graefes Arch Clin Exp Ophthalmol. 2012;250:1737–44],
non abbastanza valutati e poco usati

Criteri per estendere



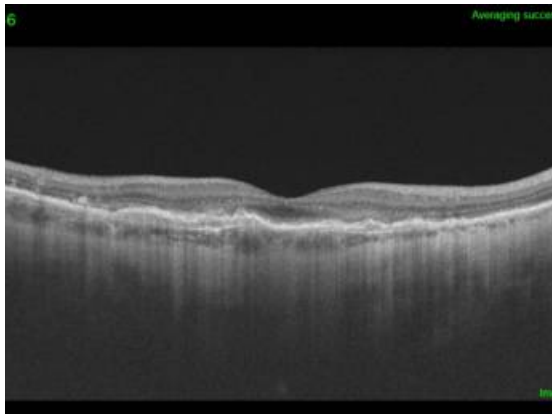
Massima acuità visiva raggiunta

Nota: Brolucizumab non consente W4 dopo la induzione di 3 IV



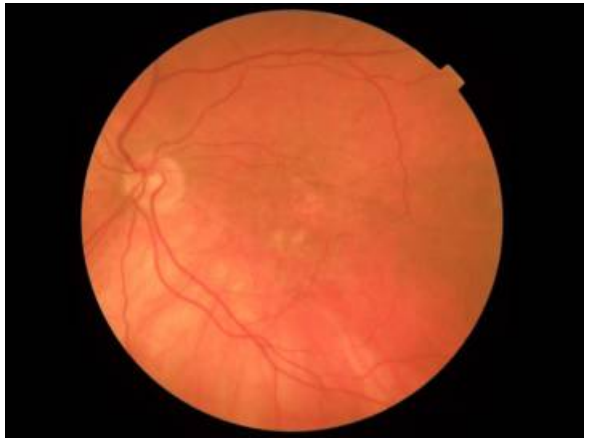
Riduzione del CRT

Nota: del basale, della media dei due precedenti, del precedente?



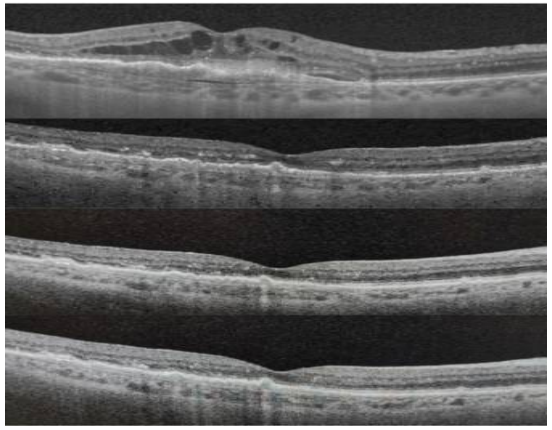
Risoluzione dei fluidi (IRF/SRF)

”Drying”



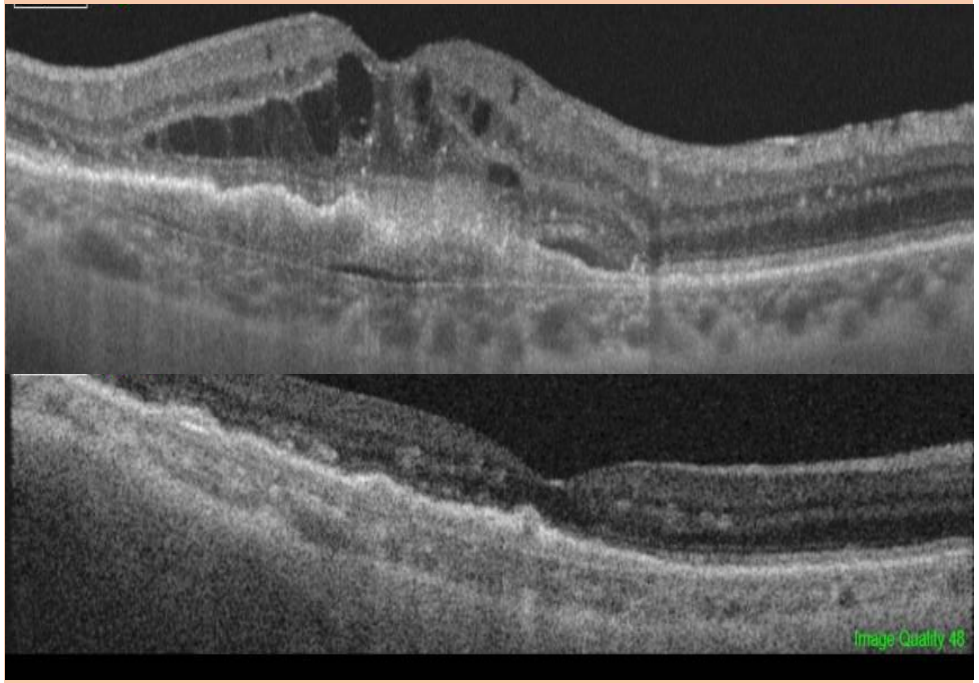
Non nuove emorragie, nv

Esame del fundus, retinografia



Stabilità per tre controlli successivi?

COME E FINO A QUANTO SI PUO' ESTENDERE??



Ranibizumab
+2 sett. max
Fino a 4 / max ?

Aflibercept 2 mg
prima estensione 8w poi +2/4 sett.; min 8 /max 20 *

Aflibercept 8 mg
prima estensione fino a 20w min 8 /max 25 **

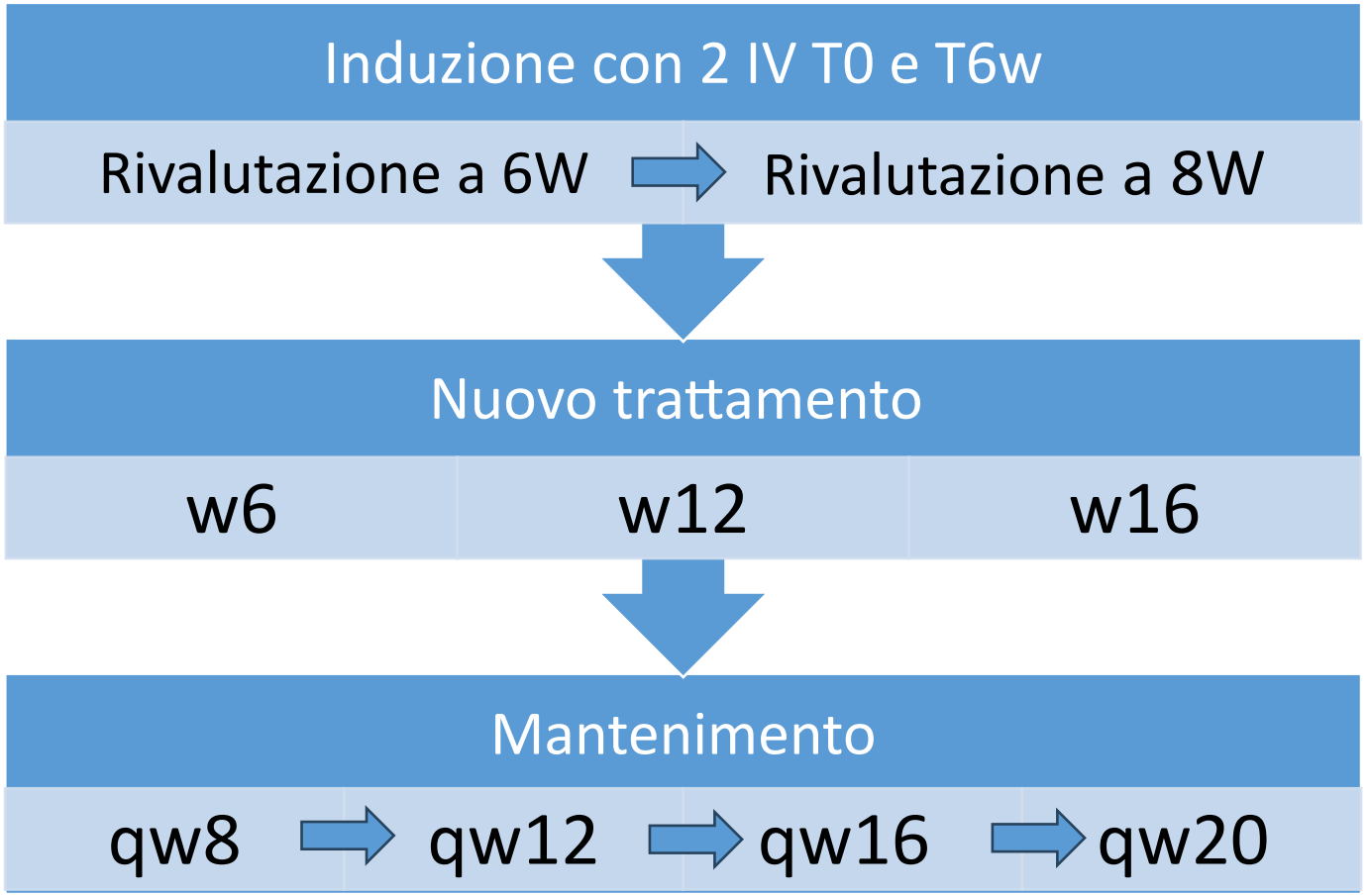
Brolucizumab
+4 sett.; min 8 /max 16 *

Faricimab
prima estensione fino a 16w**; min 8 /max …..

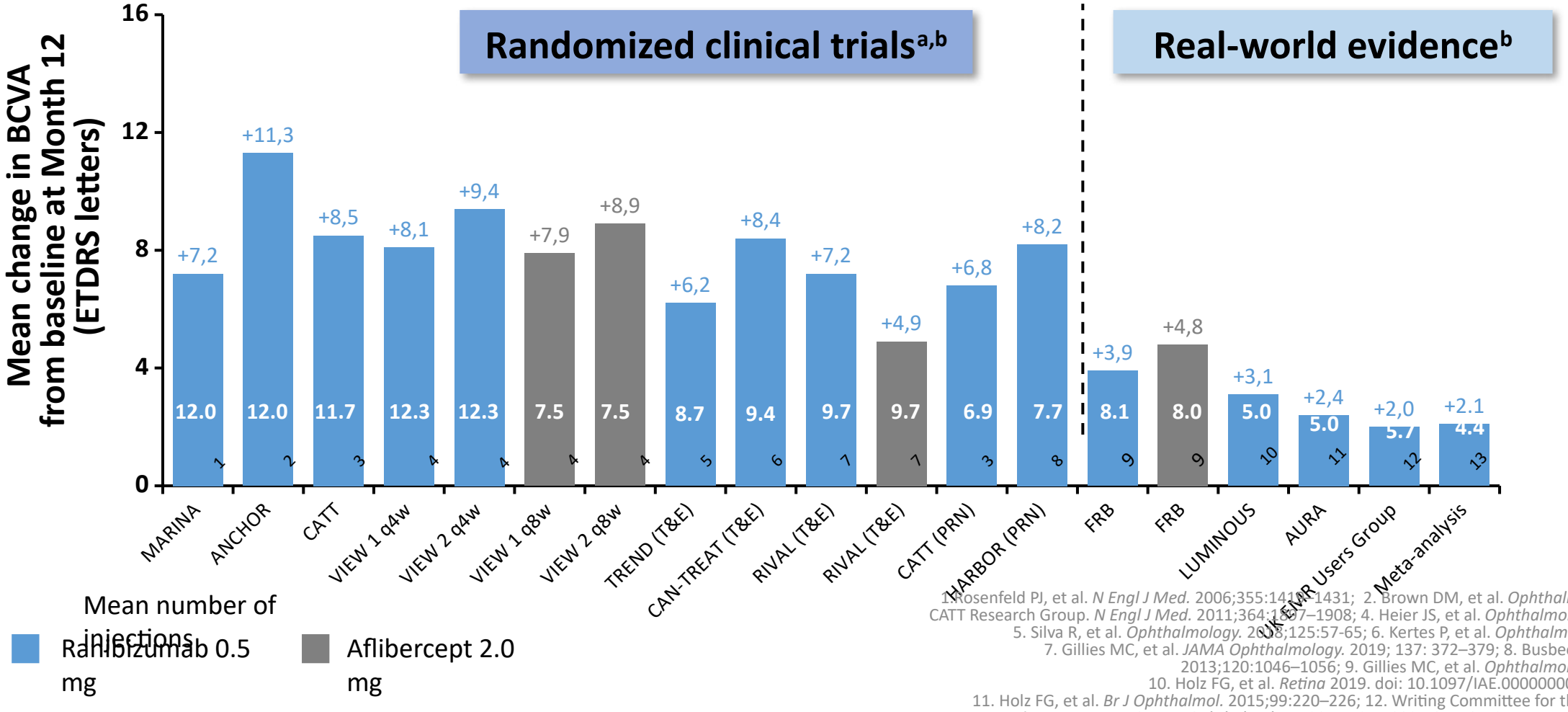
* intervalli inferiori a 4w non sono stati studiati
** 8w -12w -16w immediato

Nuovo T&E Brolucizumab

- Intervallo minimo 4 settimane
- Risultati limitati per intervalli oltre 20 settimane



Sub-optimal vision gains are observed in real-world settings compared to randomized clinical trials



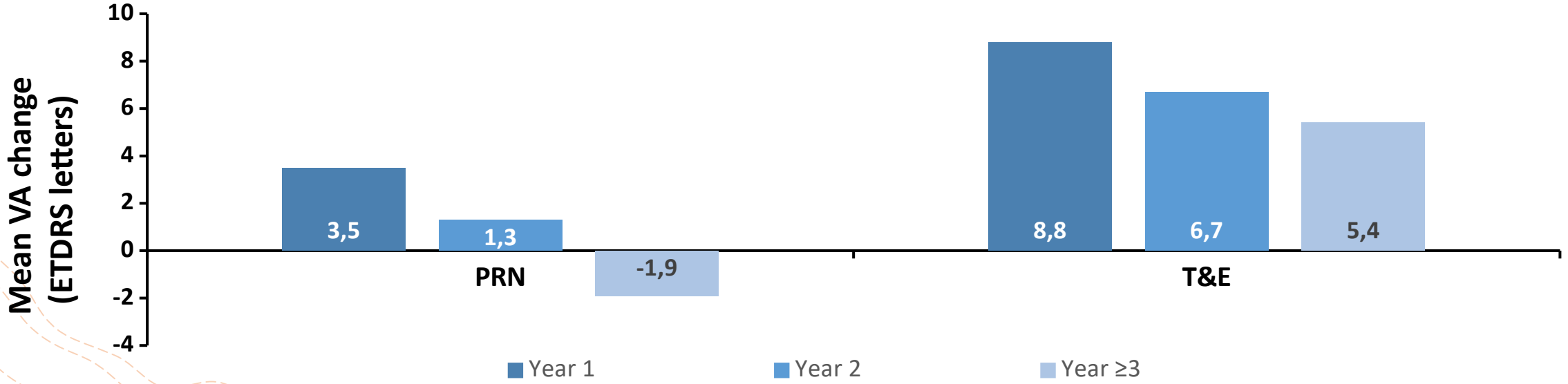
1. Rosenfeld PJ, et al. *N Engl J Med.* 2006;355:1419–1431; 2. Brown DM, et al. *Ophthalmology.* 2009;116:57–65;3. CATT Research Group. *N Engl J Med.* 2011;364:1897–1908; 4. Heier JS, et al. *Ophthalmology.* 2012;119:2537–2548; 5. Silva R, et al. *Ophthalmology.* 2018;125:57-65; 6. Kertes P, et al. *Ophthalmology.* 2019;126: 841–848; 7. Gillies MC, et al. *JAMA Ophthalmology.* 2019; 137: 372–379; 8. Busbee BG, et al. *Ophthalmology.* 2013;120:1046–1056; 9. Gillies MC, et al. *Ophthalmology.* 2016;123:2545-2553; 10. Holz FG, et al. *Retina* 2019. doi: 10.1097/IAE.0000000000002670 [ahead of print] 11. Holz FG, et al. *Br J Ophthalmol.* 2015;99:220–226; 12. Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group, *Ophthalmology.* 2014;121:1092-101; 13. Kim LN, et al. *Retina.* 2016;36:1418-31

PRN regimen – injections performed after recurrence of results in fewer injections but inferior visual outcomes compared to T&E regimen

1. Kim LN, et al. *Retina.* 2016; 36:1418-311

	8.6	9.2	8.2
	5.4	3.7	2.8

	7.8	7.6	7.0
	7.3	4.9	4.0



Meta-analysis of >26,000 patients from 42 real-world observational studies reporting outcomes of intravitreal ranibizumab for nAMD[1]

Ophthalmol Ther (2024) 13:2343–2355
https://doi.org/10.1007/s40123-024-00983-2

ORIGINAL RESEARCH

Treat-and-Extend Versus *Pro re nata* Regimens of Ranibizumab and Aflibercept in Neovascular Age-Related Macular Degeneration: A Comparative Study from Routine Clinical Practice

Eloi Debourdeau · Helene Beylerian · Vuong Nguyen · Daniel Barthelmes · Mark Gillies · Pierre Henry Gabrielle · Stela Vujosevic · Louise Otoole · Martin Puzo · Catherine Creuzot-Garcher · Benjamin Wolff · Vincent Daien · The Fight Retinal Blindness! Study Group

Eye (2017) 31, 1337–1344

www.nature.com/eye

REVIEW

A systematic review to assess the 'treat-and-extend' dosing regimen for neovascular age-related macular degeneration using ranibizumab

SR Rufai[1,2], H Almuhtaseb[1,2], RM Paul[1], BL Stuart[1], T Kendrick[1], H Lee[1,2] and AJ Lotery[1,2]

SDC OPEN

RETINA PODCAST

EFFICACY AND SAFETY OF INTRAVITREAL AFLIBERCEPT USING A TREAT-AND-EXTEND REGIMEN FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

The ARIES Study: A Randomized Clinical Trial

PAUL MITCHELL, MD, PHD,* FRANK G. HOLZ, FEBO, FARVO,† PHILIP HYKIN, FRCS, FRCOPHTH,‡ EDOARDO MIDENA, MD, PHD,§ ERIC SOUIED, MD, PHD,¶ HELMUT ALLMEIER, PHD,** GEORGE LAMBROU, MD, PHD,** THOMAS SCHMELTER, PHD,†† SEBASTIAN WOLF, MD, PHD‡‡ ON BEHALF OF THE ARIES STUDY INVESTIGATORS

RETINA 41:1911–1920, 2021

Adv Ther
https://doi.org/10.1007/s12325-020-01236-x

ORIGINAL RESEARCH

Efficacy and Safety of Intravitreal Aflibercept Treat-and-Extend Regimens in Exudative Age-Related Macular Degeneration: 52- and 96-Week Findings from ALTAIR

A Randomized Controlled Trial

Masahito Ohji · Kanji Takahashi · Annabelle A. Okada · Masato Kobayashi · Yoshimi Matsuda · Yasuhiro Terano · for the ALTAIR Investigators

AMERICAN ACADEMY OF OPHTHALMOLOGY®

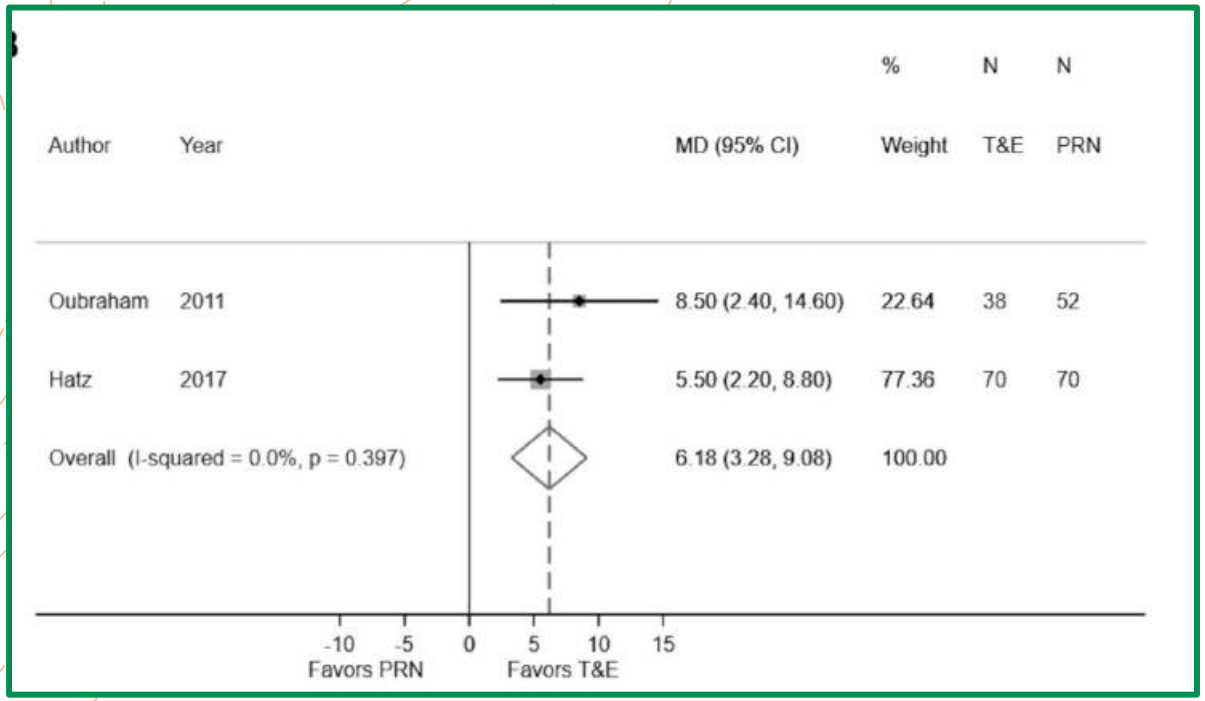
TENAYA and LUCERNE

Two-Year Results from the Phase 3 Neovascular Age-Related Macular Degeneration Trials of Faricimab with Treat-and-Extend Dosing in Year 2

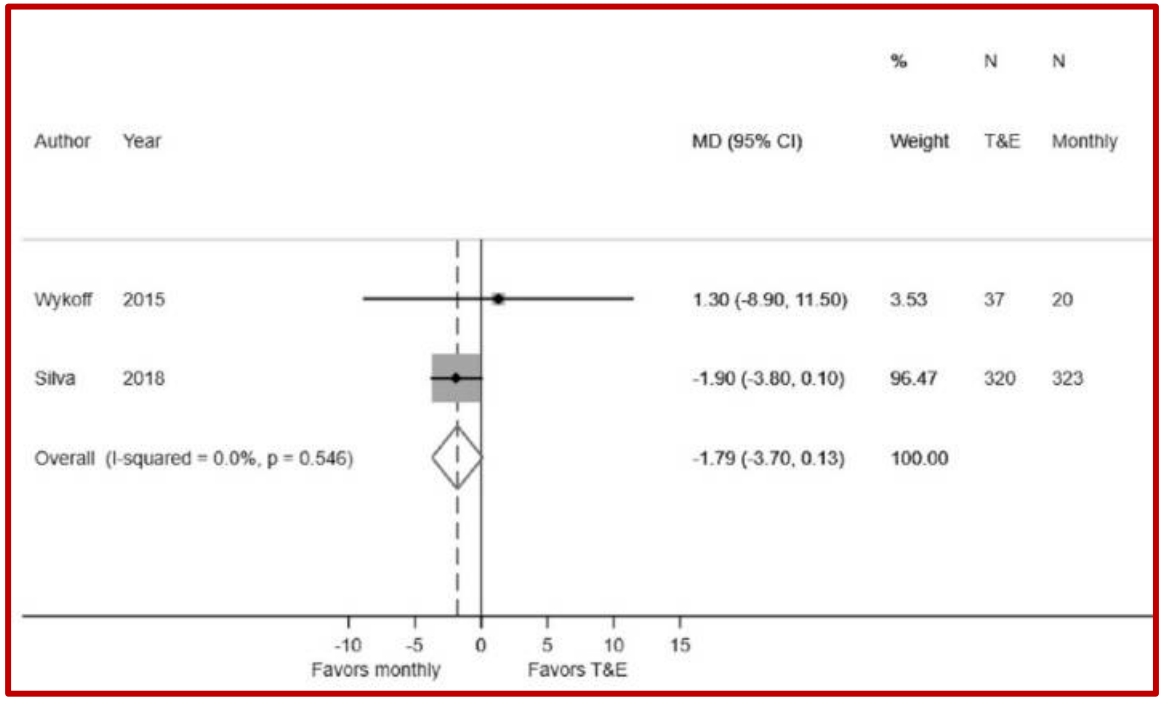
Arshad M. Khanani, MD, MA,[1] Aachal Kotecha, PhD,[2] Andrew Chang, MBBS, PhD,[3] Shih-Jen Chen, MD,[4] Youxin Chen, MD,[5] Robyn Guymer, MBBS, PhD,[6] Jeffrey S. Heier, MD,[7] Frank G. Holz, MD,[8] Tomohiro Iida, MD,[9] Jane A. Ives, MSc,[2] Jennifer I. Lim, MD,[10] Hugh Lin, MD, MBA,[11] Stephan Michels, MD, MBA,[12,13] Carlos Quezada Ruiz, MD, FASRS,[11] Ursula Schmidt-Erfurth, MD,[14] David Silverman, MSc, MBChB,[2] Rishi Singh, MD, FASRS,[15] Balakumar Swaminathan, MSc,[16] Jeffrey R. Willis, MD, PhD,[11] Ramin Tadayoni, MD, PhD,[17] for the TENAYA and LUCERNE Investigators

Ophthalmology 2024;131:914-926

T&E è più efficace del PRN
ed efficace quanto il trattamento mensile



Mean difference in improvement of BCVA



Mean difference in improvement of BCVA

M. Okada et al, Am J Ophthalmol 2018

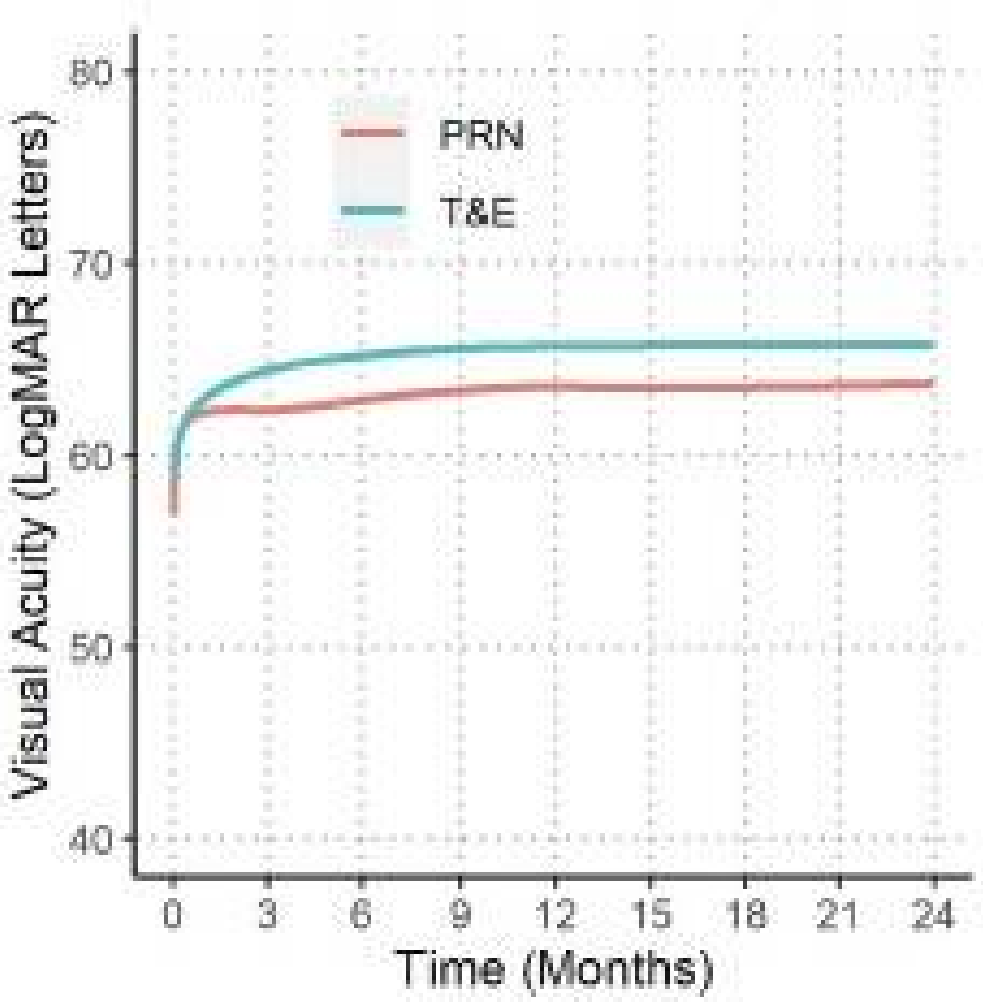
T&E è più efficace del PRN: risultati a 24 mesi del FRB

Ophthalmol Ther (2024) 13:2343–2355
https://doi.org/10.1007/s40123-024-00983-2

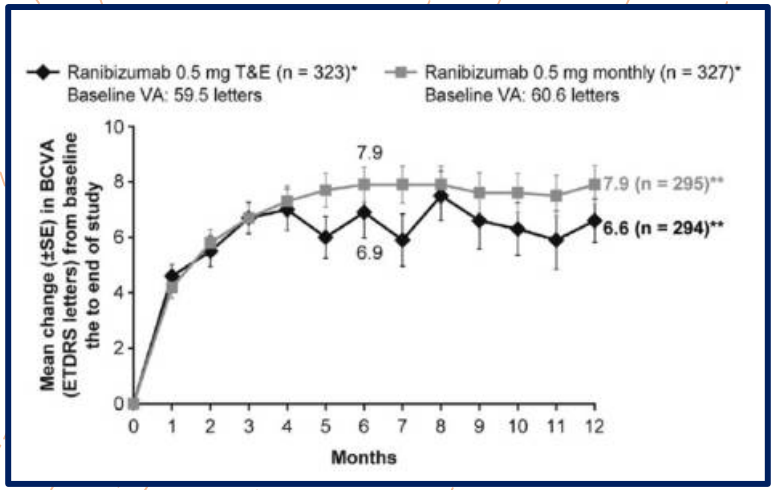
ORIGINAL RESEARCH

Treat-and-Extend Versus *Pro re nata* Regimens of Ranibizumab and Aflibercept in Neovascular Age-Related Macular Degeneration: A Comparative Study from Routine Clinical Practice

Eloi Debourdeau · Helene Beylerian · Vuong Nguyen · Daniel Barthelmes · Mark Gillies · Pierre Henry Gabrielle · Stela Vujosevic · Louise Otoole · Martin Puzo · Catherine Creuzot-Garcher · Benjamin Wolff · Vincent Daien · The Fight Retinal Blindness! Study Group

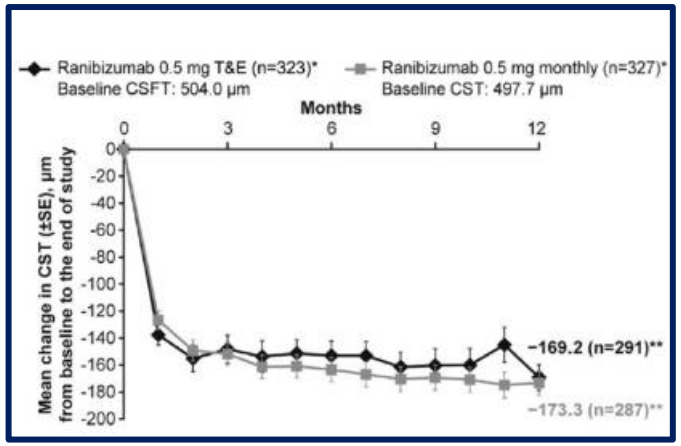


T&E T&E è efficace quanto il trattamento mensile : risultati a 12 mesi del TREND study risultati a 24 mesi del CANTREAT study

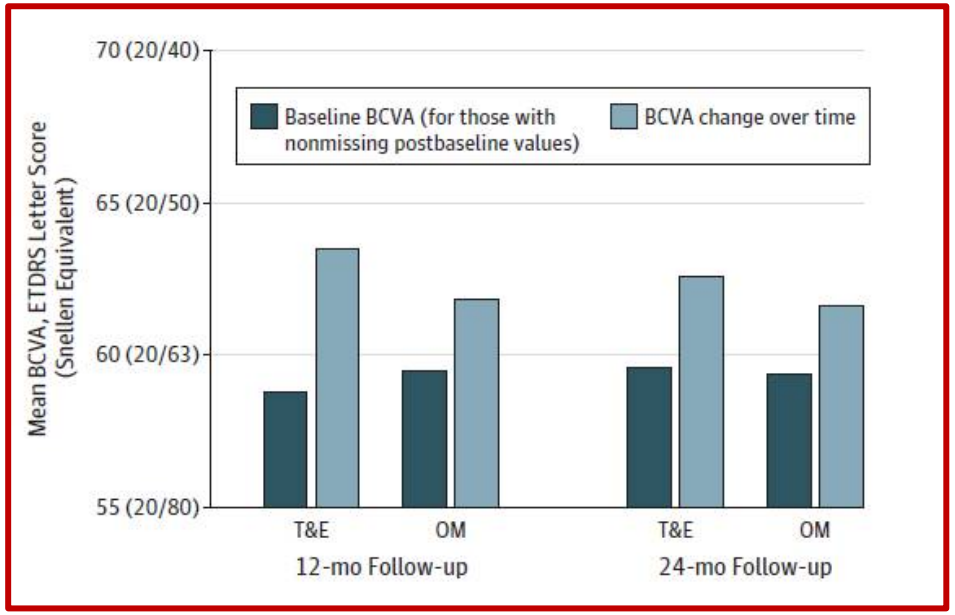


The LS mean difference between the treatment groups was 1.9 letters (95% confidence interval, 3.83 to 0.07; P < 0.001 for noninferiority).

Rufino Silva et al, Ophthalmology 2018



Difference in LS means of 2.9 µm (95% confidence interval, 14.76 to 20.53; P = 0.748



Month 24: mean BCVA improvement was not worse in the T&E treatment group (6.8 [14.1] letters) compared with the monthly treatment group (6.0 [12.6] letters; difference, 0.9; 95% CI, −1.6 to 3.3; *P* = .21)
Month 24: lower mean number of injections for T&E (17.6) compared with the monthly dosing regimen (23.5) (difference, 5.9, 95% CI, 5.4-6.5; *P* < .001).

Peter J. Kertes et al, Jama Ophthalmology 2020

GUADAGNO AV A 3 ANNI SECONDO REGIME DI TRATTAMENTO

Modified from Table 4 in Meta-analysis of real-world outcomes of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration (Kim et al., 2016). VA = Visual acuity. ΔVA = Change in visual acuity. CI = Confidence Interval.

Treatment Regimen	Baseline VA (95% CI)	ΔVA at 1 year (95% CI)	ΔVA at 2 year (95% CI)	ΔVA at 3 year (95% CI)	Mean Yearly Injections (95% CI)
Overall	53.6 (51.0–56.2)	+5.0 (3.4–6.6) n = 24,039	+3.4 (0.9–5.8) n = 17,928	+1.1 (-5.3 to 7.5) n = 13,012	5.4 (4.6–6.2)
PRN (n = 21,612)	53.0 (50.0–56.0)	+3.5 (2.0–5.0) n = 20,247	+1.3 (-1.6 to 4.2) n = 14,408	−1.9 (-9.8 to 6.0) n = 11,714	4.7 (4.0–5.5)
Treat-and-extend (n = 2566)	52.0 (46.5–57.6)	+8.8 (5.8–11.8) n = 1539	+6.7 (3.2–10.1) n = 2521	+5.4 (-4.1 to 14.9) n = 1298	6.9 (5.6–8.2)

A systematic review and meta-analysis compared the safety outcomes of T&E, fixed, and PRN dosing regimens

T&E vs. fixed[1]

- CANTREAT[2]
  - 2.7% of fixed monthly (8/293) patients withdrew because of AEs at Month 24
  - 1.4% of T&E (4/287) patients withdrew because of AEs at Month 24
- ARIES[3]
  - 0% of patients in T&E arm developed serious ocular AEs at Year 1
  - 2.2% of patients in the fixed 2q8 arm developed serious ocular AEs at Year 1

T&E vs. PRN[1]

- Hatz, *et al*.[3]
  - Vision-threatening or recurrent hemorrhage observed in 32.9% of patients in the PRN cohort
  - No ocular events were reported in the T&E cohort
- Oubraham, *et al*.[4]
  - Severe hemorrhage reported in 2 patients assigned to PRN treatment
  - No serious ocular events were reported in the T&E cohort

2q8, 2 mg every 8 weeks. AE, adverse event. PRN, *pro re nata* (as needed). T&E, treat-and-extend.

E in ospedale?

Table 1. Comparison of the three regimens most frequently employed for the administration of intravitreal anti-VEGF therapy.

Feature	Regimen		
	Pro Re Nata (PRN)	Treat and Extend (T&E)	Fixed retreatment schedule
Type of approach	Reactive	Proactive	Proactive
Monitoring visit	Monthly	The intervals between visits depend on the visit result and progressively increase (up to 12 weeks); a delay is not allowed	At regular intervals (monthly or bimonthly)
Injection administration	Only during active disease, decided every time by the ophthalmologist	On the same day of the monitoring visit; independent of disease activity	At regular intervals (monthly or bimonthly)
Advantages	Lowest number of IVIs	Establish an individual patient's optimal treatment interval to avoid recurrence of disease activity Reduced number of visits and injections versus the monthly regimen Lower burden for the patient	Possibility to plan visits and IVIs
Disadvantages	Not to miss recurrence, monthly visits are still required; a delay may affect visual outcomes Time- and resource-consuming Patient's compliance for monthly monitoring visit may be low Logistic problems linked to the uncertainty of performing injection Psychological burden for the patient due to the uncertainty of performing injection Poor functional results in real-world studies	Requires a one-stop clinic allowing for the same day visits and injections	Does not account for the high inter-variability of treatment need (frequent undertreatment in those with high need and overtreatment in those with low need)

VEGF: vascular endothelial growth factor; IVIs: intravitreal injections.

Avitabile T. et al. Eur J Ophthalmol 2020;30(4):795-804

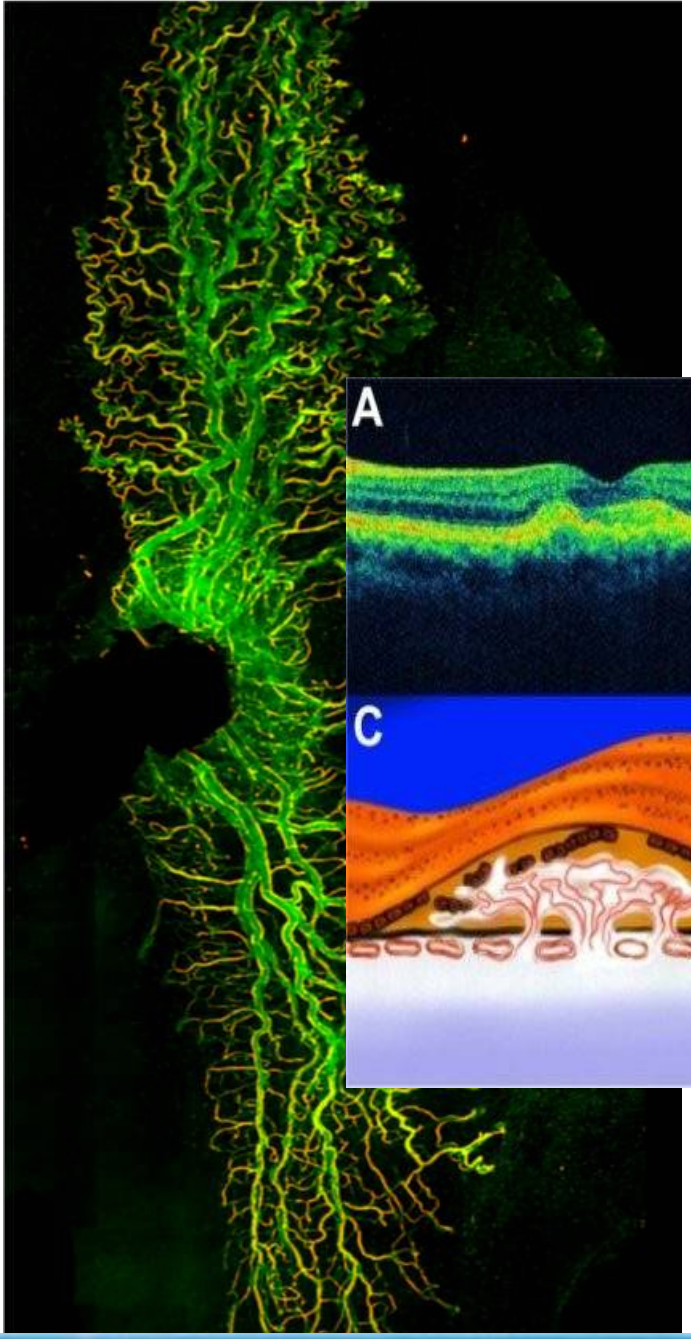
Shahzad *et al. Systematic Reviews* (2023) 12:92
https://doi.org/10.1186/s13643-023-02261-x

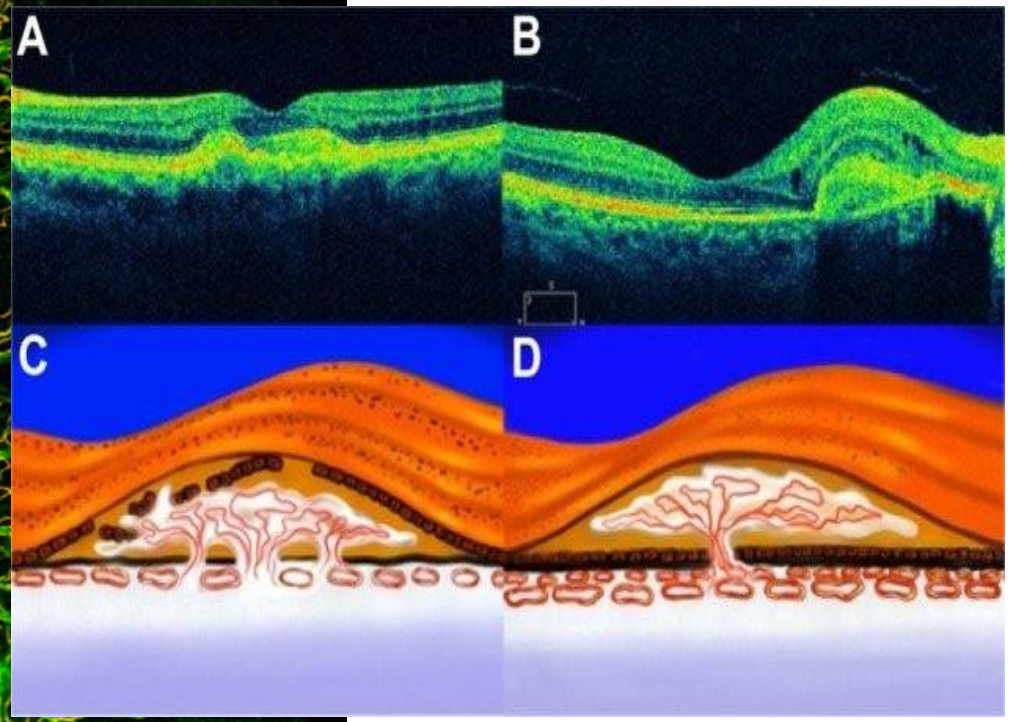
Systematic Reviews

RESEARCH Open Access

Non-adherence and non-persistence to intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy: a systematic review and meta-analysis

Haris Shahzad[1*†], Sajid Mahmood[2†], Sean McGee[3†], Jessica Hubbard[3†], Sayeed Haque[4], Vibhu Paudyal[5], Alastair K. Denniston[6,7,8,9,10], Lisa J. Hill[3†] and Zahraa Jalal[5†]





RIEPILOGO

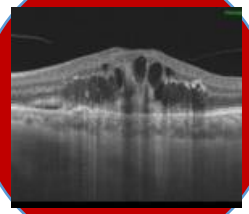
LA SCELTA DEL REGIME DI TRATTAMENTO TROVA BASE SU:

- ✓ EVIDENZE CLINICHE
- ✓ MIGLIORE CAPACITA' DI SODDISFARE LE ESIGENZE CLINICHE DEL PAZIENTE
- ✓ MIGLIORE CAPACITA' DI ORGANIZZAZIONE DELLA STRUTTURA

LA PERSONALIZZAZIONE DEL TRATTAMENTO TROVA OGGI LA MIGLIORE RISPOSTA NEL REGIME DI **TREAT AND EXTEND**

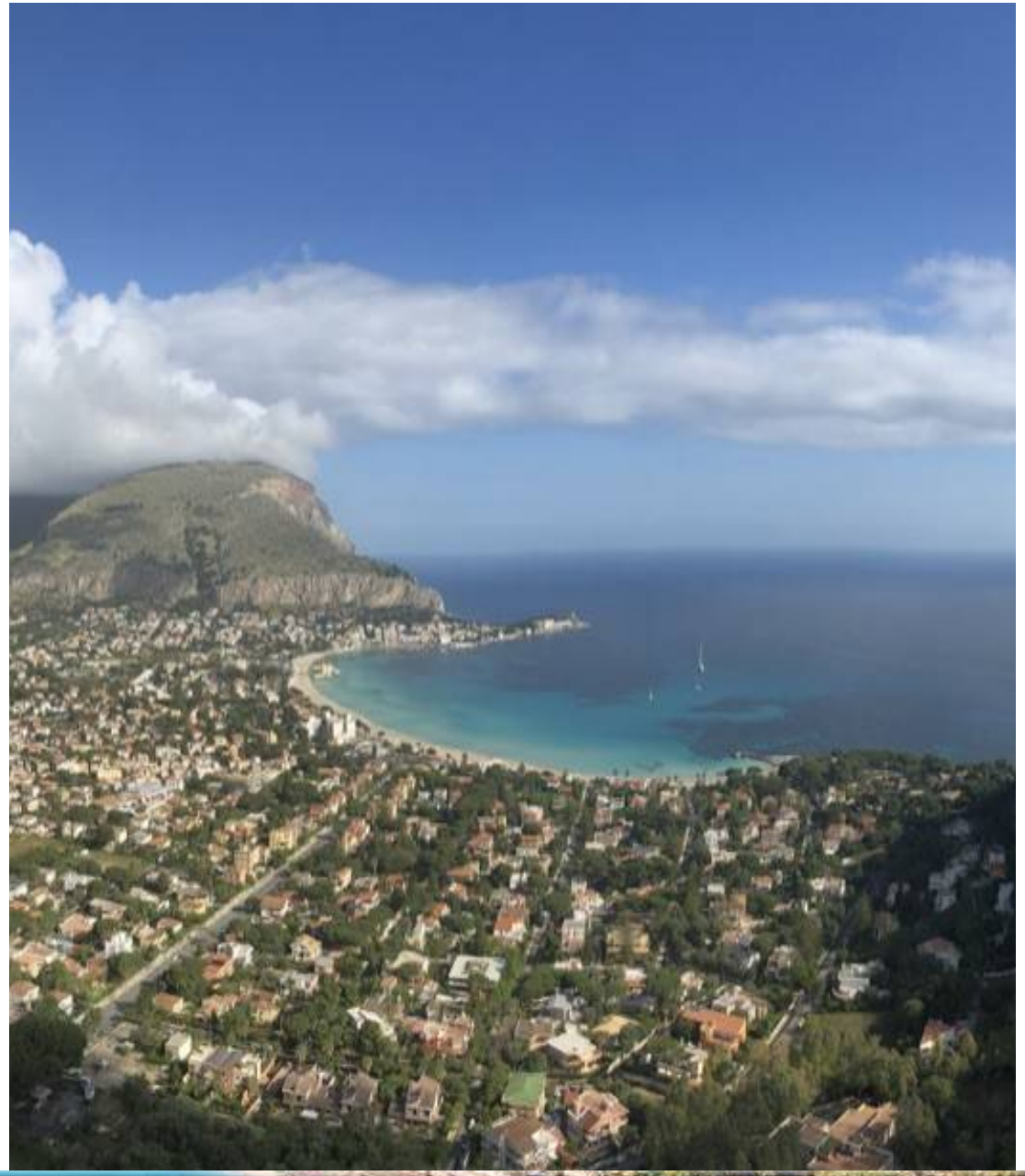
ConclusionI

La AV può essere preservata nel tempo se il paziente viene trattato in modo più intensivo e proattivo



L'uso di biomarcatori clinici per la decisione e la gestione del protocollo ottimale per ciascun paziente (personalizzato) è oggi una metodologia clinica supportata da evidenze forti.

Il traguardo è il risultato anatomico-funzionale con meno iniezioni e visite per raggiungere livelli più elevati di appropriatezza, con vantaggio organizzativo ed economico.



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