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SHORT REPORT

Tailored Anti-VEGF Therapy with New Generation Optimizations (TANGO) Treatment Regimen for Neovascular Age-Related Macular Degeneration: Rationale, Design, and Simulation Study

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Purpose: To present the rationale and design of the Tailored Anti-VEGF therapy with New Generation Optimizations (TANGO) treatment regimen for neovascular age-related macular degeneration and to simulate potential number of visits and injections with TANGO and compare to other treatment regimens.

Methods: This is a descriptive short report of the rationale and design of TANGO. The purpose of TANGO is to lessen the burden of therapy with new generation anti-VEGF medications that have better durability. We also simulate the potential number of visits and injections during the first year with TANGO and compare these numbers to other treatment regimens.

Results: Our report describes TANGO and provides a flow chart for its use. Our simulations suggest that TANGO may lead to a reduced number of visits and injections.

Conclusion: Our simulations suggest that employing TANGO may lead to a reduced number of visits and anti-VEGF injections while still providing intensive therapy for those who require it. However, it should be emphasized that this is a descriptive report and a simulation study, and clinical real-world studies of efficacy and safety using TANGO are warranted to better understand implications of employing TANGO in routine clinical practice.

Keywords: neovascular age-related macular degeneration, anti-VEGF, treatment regimen, faricimab, aflibercept, tailored anti-VEGF therapy with new generation optimizations

Introduction

Anti-VEGF therapy has dramatically improved the prognosis for patients with neovascular age-related macular degeneration (AMD).[1,2] Since its introduction, clinicians have been able to prevent irreversible blindness and provide functional vision for a large proportion of patients.[3,4] However, anti-VEGF therapy also puts a heavy treatment burden on patients and healthcare systems. Analyses based on demographic projections forecast an ever-growing number of patients with neovascular AMD and anti-VEGF injections.[5–7] Although fixed dosing regimens (ie, monthly or bimonthly injections) provide excellent clinical outcomes, they also introduce a heavy treatment burden.[8] Efforts to personalize treatment through various treatment regimens have led to a reduced number of injections and required visits while also delivering comparable clinical outcomes.[9] The *pro re nata* (PRN) regimen is based on treating only when the macula shows signs of exudative activity. The treat-and-extend (T&E) regimen begins with a loading dose and then extends the treatment interval based on the presence of activity. The observe-and-plan (O&P) regimen follows the same principles as the T&E regimen but with the important difference that the patient is observed without treatment if the macula is dry

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after the loading dose. Such treatment regimens allow for longer treatment intervals for individuals that do not require monthly or bimonthly treatment and thereby lead to reduced burden of therapy.

New generation anti-VEGF therapy using medications such as aflibercept 8 mg (Eylea HD®, Bayer, Leverkusen, Germany) or faricimab 6 mg (Vabysmo ®, Roche, Basel, Switzerland) provides extended durability that allows treatment up to 16 weeks between injections.[10–12] Aflibercept 8 mg has been tested in the PULSAR study with injection intervals even longer than 16 weeks.[12] Clinical evidence regarding faricimab treatment suggests that during the extension phase, a significant number of eyes are injected while being dry until the long interval is achieved.[10]

In our clinic, we shifted from using aflibercept 2 mg to faricimab 6 mg as first-line therapy for neovascular AMD. We built upon our good previous experiences with the observe-and-plan regimen with aflibercept 2 mg,[13] considered that faster extension rates (4-weekly adjustments) are safe even with aflibercept 2 mg,[14,15] and considered the findings from clinical studies where a large proportion of patients were treated even when the macula was dry while on new generation anti-VEGF therapy.[10] Based on these experiences, we designed a new treatment regimen for neovascular AMD, *Tailored Anti-VEGF therapy with New Generation Optimizations* (TANGO), which aims to reduce the treatment burden using several means (Figure 1).

In TANGO, after the loading dose with 3 monthly injections, a follow-up examination is scheduled 8 weeks after the last injection. The reason for scheduling follow-up 8 weeks after the last injection rather than 4 weeks is that aflibercept 8 mg and faricimab 6 mg provide a better durability than previous generation anti-VEGF medications.[10–12] At this "loading dose follow-up", TANGO distinguishes between 3 possible scenarios: 1. improvement and the macula is dry, 2. some improvement, but the macula is not dry and 3. worsening or no improvement. In the first scenario, if the macula is dry, the patient is scheduled for a follow-up in 6 weeks without treatment. Upon recurrence, the patient will receive treatment again, but if the macula stays dry further observation is scheduled with 6-weekly windows (Figure 1). In the second scenario, an improvement but not complete dry macula may reflect either a process of continuous improvement or a perhaps slight undertreatment. Considering the durability and the good effect of long treatment intervals in previous studies,[10–12] the TANGO protocol suggests that in this scenario, 3 injections are scheduled with 8-weekly intervals. In the third scenario, a worsening at 8 weeks after the last injection may indicate a need for a shorter interval. The interval is therefore decreased with 2 weeks and the TANGO protocol suggests that in this scenario, 3 injections are scheduled with 6-weekly intervals. In the following follow-up visits, as a general rule, the interval is decreased with 2 weeks when there is evidence of exudative activity, whereas when the macula is dry, the interval is extended with 4 weeks. This way, TANGO pushes the treatment towards longer intervals. Another important means to reduce the burden is that we schedule injections in series of 3 or 2 (3 injections up to 12-weekly intervals and 2 for 14-, and 16-weekly intervals), and follow-ups only after the last injection in the series. With TANGO, we also acknowledge the chronicity and regular patterns in some patients and suggest the use of up to 6 injections with the apparent interval pattern until the next follow-up visit. In addition, if the treatment response is insufficient and the patient is repeatedly treated at 6-weekly intervals, TANGO systematizes switching to other anti-VEGF medication so that switching can be considered in a systematized manner in the treatment regimen.

In this short report, we present our new treatment regimen TANGO for neovascular AMD through which we aim to lessen the burden of therapy using new generation anti-VEGF medications. We also present a simulation study to evaluate the number of follow-up visits and the number of injections using TANGO and other treatment regimens for neovascular AMD.

Methods

This short report simulates the number of visits and anti-VEGF injections during the first year (52 weeks) of therapy. According to Danish law, approvals are not needed for simulation studies. We simulated numbers of visits and injections based on two types of fixed dose regimens, two types of *pro re nata* (PRN) regimens, the treat-and-extend (T&E) regimen, the observe-and-plan (O&P) regimen, and the TANGO regimen. For all regimens, we assumed a loading phase with 3 monthly injections.

For the fixed dose regimens, we assumed one baseline visit, one follow-up 4 weeks after the loading dose (ie, 12 weeks after treatment start), and one follow-up 52 weeks after treatment start. After the loading dose, we simulated injections every 4 weeks in one fixed dose regimen and every 8 weeks in another fixed dose regimen.

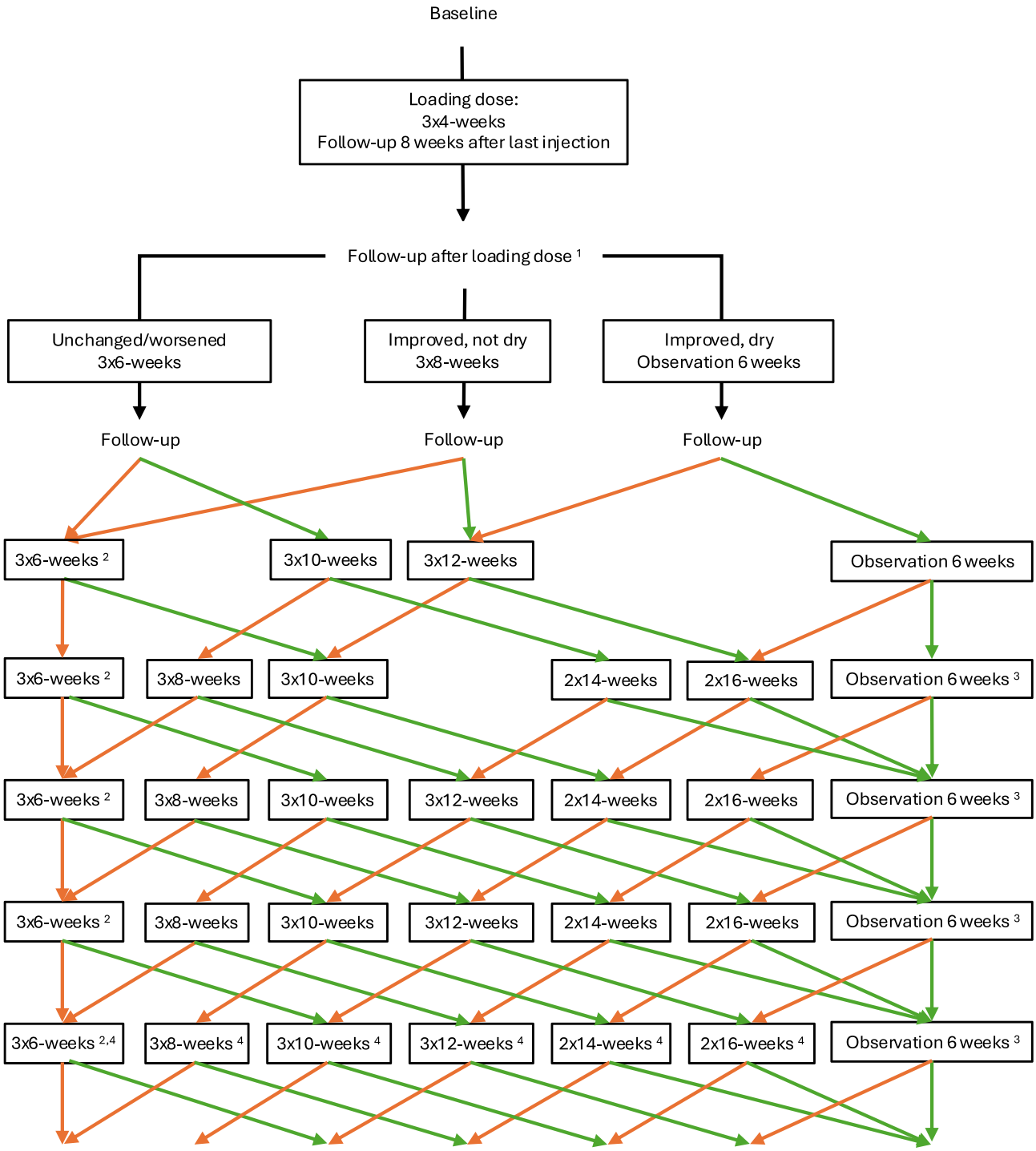

Figure 1 The Tailored Anti-VEGF therapy with New Generation Optimizations (TANGO) treatment regimen protocol for neovascular age-related macular degeneration. At follow-up after loading dose (8 weeks after the last injection), no change/worsening leads to 3 injections with 6-weeks interval, improvement without dry macula leads to 3 injections with 8-weeks interval, and dry macula leads to observation for 6 weeks. At later follow-ups, Orange arrows indicate exudative activity and intensification of therapy, and green arrows indicate dry macula. Annotations: 1 Since some patients can be deemed intractable after loading dose, extra attention should made to discharge patients after loading dose who no longer fulfill treatment criteria; 2 In cases of persisting fluid despite intensive therapy, we suggest reconsidering the diagnosis and considering performing a fluorescein and indocyanine green angiography, and also considering changing to another anti-VEGF agent; 3 If the macula has been dry for 6 months/26 weeks, the patient is discharged from the hospital for further follow-ups at a local primary care ophthalmologist; 4 If a certain pattern of exudative activity is apparent, we suggest to consider up to 6 injections with the identified interval and only adjust the interval with ±1–2 weeks if needed.

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For the PRN regimens, we assumed one baseline visit and one follow-up 4 weeks after the loading dose (ie, 12 weeks after treatment start). Two types of PRN regimens were defined, which differed in their design after loading dose. One type of PRN regimen (PRN1) was defined as follow-up visits every 4 weeks after the loading dose at which 0–1 injection could be planned. Another type of PRN regimen (PRN2) was defined as visits every 12 weeks at which 0–3 injections could be planned based on the activity level at the discretion of the treating physician.

For the T&E regimen, we assumed one baseline visit and one follow-up 4 weeks after the loading dose (ie, 12 weeks after treatment start). After the loading dose, we simulated that in case of exudative activity, an injection could be given and a follow-up visit 4 weeks after could be planned, whereas in case of dry macula an injection could be given, and a follow-up visit 6 weeks after could be planned. Further treatments could be planned with shortening or extension of the interval with ±2 weeks depending on the activity, but no shorter than 4 weeks and no longer than 16 weeks. Depending on the activity, this would lead to 5–9 further injections and 5–9 further follow-up visits. A flow chart of the T&E regimen is available as Supplementary File 1.

For the O&P regimen, we assumed one baseline visit and one follow-up 4 weeks after the loading dose (ie, 12 weeks after treatment start). After loading dose, we simulated that in case of exudative activity, 3 injections could be given with an interval of 4 weeks and a follow-up visit 4 weeks after the last injection (ie, 24 weeks after treatment start), and in case of dry macula, observation every 4 weeks. In the group with active therapy, treatment interval could be shortened (to a minimum of 4 weeks) or extended by 2 weeks depending on the activity at the next follow-up visit, which would then lead to 1–2 further follow-up visits and 3–6 further injections within the first year. In the group that is observed without therapy because of dry macula after the loading dose, number of visits and injections would depend on the following recurrence of the activity. In case of dry macula throughout all follow-ups, this would lead to 9 additional follow-up visits and 0 additional injections. In case of exudative activity at the 2nd or 3rd follow-up (ie, 8 or 12 weeks, respectively, after the last injection of the loading dose), 3 injections could be given with an interval of 6 weeks and a follow-up visit 6 weeks after the last injection (ie, 50 or 54 weeks, respectively, after treatment start). Treatment interval could be shortened or extended by 2 weeks depending on the activity. Regardless of the interval decided, this would lead to 0–1 additional injections within the first year of therapy. In case of dry macula during observation until exudative activity at the 4th to 6th follow-up (ie, 16 or 24 weeks, respectively, after the last injection of the loading dose), 2 injections could be given with an interval of 10 weeks and a follow-up visit 10 weeks after the last injection, however, within the first year, this would lead to 2 additional injections and 0–1 additional follow-up visits. A flow chart of the O&P regimen is available as Supplementary File 2.

For the TANGO regimen, we assumed one baseline visit and one follow-up 8 weeks after the loading dose (ie, 16 weeks after treatment start). After loading dose, we simulated that in case of unchanged/worsened exudative activity, 3 injections could be given with an interval of 6 weeks and a follow-up visit 6 weeks after the last injection (ie, 34 weeks after treatment start), in case of improvement without dry macula, 3 injections could be given with an interval of 8 weeks and a follow-up visit 8 weeks after the last injection (ie, 40 weeks after treatment start), and in case of dry macula, observation every 6 weeks. In case of dry macula throughout all follow-ups, this would lead to 6 additional follow-up visits and 0 additional injections. Remaining categories would require follow-up visits and additional injections depending on the activity (Figure 1). In summary, 1–6 additional follow-up visits after the follow-up after loading dose and 0–6 additional injections after the loading dose can be expected.

Results

Number of examination visits within the first year of anti-VEGF therapy were 3 for fixed dose every 4 weeks, 3 for fixed dose every 8 weeks after completion of loading dose, 12 for PRN1, 5 for PRN2, 7–12 for T&E, 3–9 for O&P, and 3–9 for TANGO.

Number of injections within the first year of anti-VEGF therapy were 12 for fixed dose every 4 weeks, 8 for fixed dose every 8 weeks after completion of loading dose, 3–12 for PRN1, 3–12 for PRN2, 8–12 for T&E, 3–12 for O&P, and 3–9 for TANGO.

Table 1 Comparison of Simulated Number of Examination Visits and Injection Visits With Different Anti-VEGF Treatment Regimens

	Examination Visits, N	Injection Visits, N	Any Events (Examination and Injection Visits on Separate Days), N	Any Events (Examination and Injection Visits on Same Day When Possible), N
Fixed dose every 4 weeks	3	12	15	12
Fixed dose every 8 weeks after completion of loading dose	3	8	11	8
Pro re nata, protocol 1	12	3–12	15–24	12
Pro re nata, protocol 2	5	3–12	8–17	5–12
Treat-and-extend	7–11	8–12	12–20	8–12
Observe-and-plan	3–9	3–12	11–16	9–12
TANGO	3–9	3–9	8–12	6–9

Notes: *Pro re nata* protocol 1 was defined as follow-up visits every 4 weeks after the loading dose at which 0–1 injection could be planned based on the activity level. *Pro re nata* protocol 2 was defined as visits every 12 weeks at which 0–3 injections could be planned based on the activity level.
Abbreviation: TANGO, Tailored Anti-VEGF therapy with New Generation Optimizations TANGO.

Total number of any events (follow-up visits and injections) within the first year of anti-VEGF therapy were 15 for fixed dose every 4 weeks, 11 for fixed dose every 8 weeks after completion of loading dose, 15–24 for PRN1, 8–17 for PRN2, 12–20 for T&E, 11–16 for O&P, and 8–12 for TANGO. Total number of any events, when allowing for examination and injection same day where possible were 12 for fixed dose every 4 weeks, 8 for fixed dose every 8 weeks after completion of loading dose, 12 for PRN1, 5–12 for PRN2, 8–12 for T&E, 9–12 for O&P, and 6–9 for TANGO.

These simulated numbers of examination visits and number of injections are summarized in Table 1.

Discussion

In this short report, we presented the rationale and design of our new treatment regimen TANGO for neovascular AMD. Our simulation exercise showed that the number of any events (ie, examination visits and injections) with TANGO within the first year had a range that were comparable to that of O&P, although the minimum number of any events during the first year was lowest in TANGO.

In a real-world study of aflibercept 2 mg in an O&P regimen, we reported detailed aspects of the impact of O&P regimen on the burden of therapy.[13] We found that 41.3% had a dry macula and could undergo monthly observation without treatment, and of these, 49.2% and 34.0% remained dry after 3 and 6 months, respectively.[13] These results illustrate that the number of injections can be reduced in a meaningful manner with an observation plan for eyes that are dry after completion of the loading dose. In that study, a median of 7 injections were given during the first year.[13] After 1 year, the median injection interval was 6 weeks, and only 3.1% of eyes in active anti-VEGF treatment were extended to 12 weeks.[13] In a real-world study of the new generation anti-VEGF, faricimab 6 mg, Modeste et al reported that after 10 months and with a T&E protocol with 2-weeks interval adjustment plan, the mean number of injections was 6.6 and that 28.8% of eyes was able to be extended to 16 weeks at the end of the study period.[16] Matsumoto et al reported that after 1 year of faricimab 6 mg treatment and with a T&E protocol with 4-weeks interval adjustment plan, the mean treatment interval was 12.7 weeks.[17] Thus, treatment with faricimab 6 mg may result in a higher likelihood of achieving dry macula, which enables a 4-week interval adjustment plan to facilitate rapid extensions for those who are eligible for longer intervals. No studies have reported outcomes of faricimab in an O&P or TANGO regimen, however, given the initial real-world clinical evidence, we speculate that a newer generation anti-VEGF therapy using faricimab 6 mg or aflibercept 8 mg may lead to an important number of cases that may be dry after loading dose and that a rapid extension protocol may allow a faster identification of the relevant interval for the

patient. One interesting challenge with newer generation anti-VEGF therapy is that while some patients still may need intensive therapy, other patients may only require injections with a very long interval. This rises a challenge for treatment regimens designed for older generation anti-VEGF therapy as they may overtreat those for whom very long treatment intervals would be sufficient.

Limitations of this study should be acknowledged when interpreting its results. It is important to highlight that this is a design, rationale, and simulation report. We do not present real-world results of clinical efficacy or burden of therapy in this paper. Potential overtreatment or undertreatment may lead to undesirable clinical outcomes. Our clinical experience so far is that cases with macular hemorrhage, severe complications, and general outcomes have not differed after implementation of TANGO; however, determination of clinical efficacy of TANGO and benefits in terms of burden of therapy require clinical studies of visual and anatomical outcomes after implementation of TANGO. In TANGO, exit from the treatment protocol can be due to patient preference, dry macula for ≥6 months/26 weeks, or intractable lesion. For context, in Denmark when patients are discharged from the hospital, primary care ophthalmologists perform follow-ups of the patients and can re-refer for therapy upon recurrence of exudation.[10,18] Thus, based on TANGO, in case of dry macula after completion of the loading dose, and four further follow-up visits with dry macula, it is possible in our setting to discharge the patient from the hospital. Other organization of the healthcare system may limit the potential organizational benefits from implementing TANGO. One such example is aspects of TANGO which can be considered off-label. Faricimab 6 mg with a loading dose of 3 injections rather than 4, and aflibercept 8 mg with 6-weeks treatment interval, are both aspects of TANGO that would be considered off-label, at least in the USA. These aspects may limit the extent to which TANGO can be applied in certain countries. In addition, comparison of treatment regimens designed and based on experiences using previous anti-VEGF medications gives TANGO perhaps an unfair advantage in terms of number of visits as TANGO does not treat with 4-weekly intervals after the loading dose. Furthermore, TANGO does not deal with how activity is evaluated, which is at the discretion of treating physician. In our center, this is routinely done using optical coherence tomography-based evaluation of the presence of intraretinal or subretinal fluid. Cases in which there is uncertainty regarding exudative activity are subject to fluorescein angiography. Finally, while employment of treatment regimens in a systematic manner may benefit clinical organizations and services as a whole, real-world evidence finds that certain cases may need a follow-up or a treatment plan that falls outside of a treatment regimen.[19]

Conclusion

Thanks to new generation anti-VEGF medications, some of our patients experience long treatment intervals, whereas others still need intensive therapy. From an organizational point of view, a desirable treatment regimen should accommodate all patients and ease the overall burden of therapy for all. In this short report, we present our new treatment regimen TANGO through which we aim to lessen the burden of therapy using new generation anti-VEGF medications. Our simulations suggest that TANGO may deliver a reduced number of visits and injections while still providing intensive therapy for those require it. Real-life studies are underway to share experiences and outcomes of implementing TANGO, which should be considered before concluding on its clinical efficacy.

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