Anti-vascular endothelial growth factor (anti-VEGF) agents are the mainstay of therapy for treatment of neovascular age-related macular degeneration (nvAMD), one of the leading causes of blindness in the developed world. There have been a variety of different treatment regimens that have been examined for the administration of anti-VEGF therapies, including continuous fixed dosing, pro re nata administration, and treat and extend (TAE) protocols. There is no clear consensus on which dosing regimen optimizes visual and anatomical outcomes while accounting for factors such as cost and patient burden. Based on recent surveys in 2014 and 2017 by the American Society of Retina Specialists (ASRS), the majority of ophthalmology providers are utilizing TAE protocol for anti-VEGF dosing for the management of nvAMD. Although there are a number of clinical trials that have examined TAE dosing, the ALTAIR study is the first, large, prospective randomized controlled trial to compare two different TAE protocols utilizing the anti-VEGF agent aflibercept for nvAMD. The ALTAIR study, in conjunction with other previous clinical trials, suggests that TAE protocol with aflibercept is an effective anti-VEGF dosing regimen for patients with nvAMD as it produces good visual gains and minimizes cost and burden for the patient.

Keywords: Anti-vascular endothelial growth factor, Neovascular age-related macular degeneration, Treat and extend
administered as a continuous regimen of injections given monthly over a period of 24 months for patients with nvAMD. The PIER\(^6\) and EXCITE\(^7\) trials examined the efficacy of ranibizumab injections administered on a quarterly basis. Both the PIER and EXCITE trials determined quarterly injections were inferior to a monthly dosing regimen for visual acuity gains. In contrast, a PRN dosing regimen is individualized on the basis of the clinical examination and the presence of fluid; retreatment is determined based on a decrease in visual acuity or evidence of disease activity. The SAILOR\(^8\) trial examined ranibizumab administered on a PRN basis, while the CATT\(^9\) trial compared bevacizumab and ranibizumab administered PRN versus fixed monthly dosing.

The above studies showed that quarterly and PRN regimens led to less frequent monitoring and dosing for patients. The CATT\(^9\) trial showed a larger, though insignificantly different, letter gain in the fixed monthly dosing arm compared to the PRN arm. Contrarily, the PIER and EXCITE studies showed a significant decrease in visual acuity gain in the quarterly arm compared to the monthly arm.\(^6,7\) These studies showed that a less frequent dosing regimen such as PRN may be a viable alternative to monthly dosing though quarterly injections are unsatisfactory to preserve visual outcomes.

Furthermore, the HARBOR trial studied 2-year outcomes for nvAMD patients who were treated PRN after 3 months of ranibizumab injections.\(^10\) The patients in this study received anywhere from 3 to 24 injections over a 24 month period, with the median number of injections patients needed by the month 24 was 14 (\(n = 237\)). The results from this study favor the individualized unique response to anti-VEGF agents, and perhaps, the need for a regimen that is more tailored to the patient.

As evidenced in the previous studies, it is likely that a fixed, frequent dosing regimen will lead to overtreatment in some patients. Further drawbacks to a fixed dosing regimen include higher costs for potentially unnecessary treatment and a burden for the patient given the increased frequency of visits. With a greater number of injections, it also increases the risk for infection, glaucoma,\(^11\) and possibly atrophy.\(^12\) On the other hand, a PRN regimen may allow for the recurrence of neovascular leakage and growth for patients with nvAMD. Multiple recurrences can lead to further progression of the disease, which could lead to poor long-term visual outcomes in some patients.

There has been no clear consensus as for which regimen is most efficacious and cost-effective for patient outcomes. In routine clinical practice, practitioners use a variety of dosing regimens to treat nvAMD. The American Society of Retina Specialists (ASRS) survey in 2014 showed that the majority of clinicians practice with TAE protocol (78%), though some report using PRN protocol (16%), with a minority using a fixed regimen (2%).\(^13\) Furthermore, in 2017, the ASRS survey reported an increasing proportion of clinicians (70.9%) are utilizing a TAE dosing regimen to treat nvAMD patients once they have achieved dryness on their optical coherence tomography (OCT) scan.\(^14\) nvAMD is a heterogeneous disease with a variable natural history, and patients have differing response to intravitreal injections. Fixed monthly treatments are not suitable for every individual, as the degree of VEGF suppression varies between patients.

A treatment regimen that physicians are utilizing more frequently in routine clinical practice is TAE.\(^13,14\) TAE protocol involves monthly treatment with anti-VEGF until the patient is considered “dry” and with stable visual acuity. The macula is considered dry when there is no visible subretinal fluid or intraretinal cysts and the central retinal subfield thickness is no greater than 2 standard deviations from the normal of the OCT system used. If the patient is considered “dry” with stable vision, then their treatment interval can be extended appropriately by a predetermined interval. Furthermore, if the fluid recurs or their visual acuity worsens, their treatment interval is then decreased. TAE dosing is variable and therefore individualized while also allowing the patient to receive proactive continuous treatment. This review examines the major studies in the literature that have utilized TAE therapy, particularly focusing on the ALTAIR study. The ALTAIR study is the first large prospective randomized controlled trial to critically compare different TAE regimens with aflibercept.

**ALTAIR STUDY**

The ALTAIR study is a multicenter randomized open-label Phase 4 study performed in Japan at 40 clinical sites to assess two different approaches of the TAE dosing regimen.\(^15\) Although there are a number of other studies that have examined TAE regimens, previously there have been no published prospective large-scale clinical studies of patients receiving the anti-VEGF agent aflibercept using the TAE protocol or that have directly compared multiple TAE regimens.

Inclusion criteria for the study included adults aged over 50 years with treatment-naive nvAMD, active subfoveal CNV lesions seen on fluorescein angiography, and BCVA of 25 to 73 ETDRS letters (approximately 20/40-20/320 Snellen equivalent) in the study eye. 3 monthly doses of intravitreal aflibercept injections were given to each patient. Patients were then randomized to either 2-week or 4-week treatment intervals for injections. Main outcome measured was mean change in BCVA from baseline to week 52.\(^15\)

255 patients were included in the study. 124 patients were in the 2-week adjustment group and 123 patients were in the 4-week adjustment group. Patients were extended if no fluid was seen on examination, maintained at their interval if there was residual but decreased fluid, and had a shortened interval...
As summarized in (Table 1), the 2-week extension group has a mean gain of 9.0 letters, and the 4-week extension group had a mean gain of 8.4 letters at 52 weeks. 32.5% of patients in the 2-week adjustment group and 30.9% of patients in the 4-week adjustment group gained ≥ 15 ETDRS letters by 52 weeks. The last interval before the week 52 was an average of 10.7 weeks for the 2-week extension group and 11.8 weeks for the 4-week extension group. In the 2-week extension group, the last interval was >8 weeks for 72 patients (58.5%), >12 weeks for 52 patients (42.3%), and 16 weeks for zero patients. In the 4-week extension group, the last interval was >8 weeks for 74 patients (60.2%), >12 weeks for 61 patients (49.6%), and 16 weeks for 50 patients (40.7%).[15]

The 2-week extension group had an average of 7.2 injections over 52 weeks, while the 4-week extension group had an average of 6.9 injections. Based on their last visit within the 52 weeks, the length of the next scheduled interval for patients in the 2-week extension group was >8 weeks for 76 patients (68.5%), >12 weeks for 63 patients (56.8%), and 16 weeks for 39 patients (35.1%). For the patients in the 4-week extension group, the length of the next scheduled interval was >8 weeks for 76 patients (65.5%), >12 weeks for 67 patients (57.8%), and 16 weeks for 47 patients (40.5%).[15]

### COMPARISON TAE STUDIES

A number of other studies, including ALTAIR, have examined the efficacy of TAE therapy. There have been some prospective studies though the majority have been retrospective and examined the anti-VEGF agents such as ranibizumab and bevacizumab. The results of the various TAE studies are also summarized in (Table 2).

#### Prospective TAE studies with aflibercept

In addition to ALTAIR, one smaller study looked at the use of aflibercept to treat nvAMD using a TAE protocol, Aflibercept TAE for Less frequent Administration Study. This was a prospective study with 31 nvAMD patients over a 2-year period.[16] Patients received a mean number of 8 injections over the 1st year and 6.5 injections in the 2nd year. Comparable to the results of the ALTAIR study, 75% of the patients in the study had their treatment interval extended to 8 or more weeks while 38% had their treatment interval extended to 12 or more weeks.

#### Prospective studies with TAE arm with ranibizumab or bevacizumab

The LUCAS study examined TAE regimens using anti-VEGF agents ranibizumab and bevacizumab in a large prospective study with 432 patients, where patients were extended by 2 weeks at a time with a maximum interval of 12 weeks.[17] Both agents produced comparable gains in ETDRS letters (8.2 letters for ranibizumab and 8.0 for bevacizumab) and similar decreases in retinal thickness (120 µm for ranibizumab and 109 µm for bevacizumab). There was a statistically significant, though small difference, in the number of injections (8 for ranibizumab and 8.8 for bevacizumab) at 12 months. This study showed the similar efficacies of using a TAE dosing regimen with ranibizumab and bevacizumab to treat nvAMD.

The TREND study is a large prospective study with 650 patients that examined TAE versus monthly dosing using

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**Table 1: Summarized results of the ALTAIR study**

<table>
<thead>
<tr>
<th>Metrics measured in ALTAIR study</th>
<th>2-week extension group</th>
<th>4-week extension group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETDRS gain in 52 weeks</td>
<td>9</td>
<td>8.4</td>
</tr>
<tr>
<td>% who gained ≥ 15 ETDRS letters in 52 weeks</td>
<td>32.5%</td>
<td>30.9%</td>
</tr>
<tr>
<td>Average number of injections in 52 weeks</td>
<td>7.2</td>
<td>6.9</td>
</tr>
<tr>
<td>Length of last interval in weeks before week 52</td>
<td>10.7</td>
<td>11.8</td>
</tr>
<tr>
<td>Number of patients with last interval &gt;8 weeks</td>
<td>72 (58.5%)</td>
<td>74 (60.2%)</td>
</tr>
<tr>
<td>Number of patients with last interval &gt;12 weeks</td>
<td>52 (42.3%)</td>
<td>49.6 (40.7%)</td>
</tr>
<tr>
<td>Number of patients with last interval 16 weeks</td>
<td>0 (0%)</td>
<td>50 (40.7%)</td>
</tr>
<tr>
<td>Length of next scheduled interval in weeks determined at last visit</td>
<td>12</td>
<td>12.1</td>
</tr>
<tr>
<td>Number of patients with next interval determined as &gt;8 weeks</td>
<td>76 (68.5%)</td>
<td>76 (65.5%)</td>
</tr>
<tr>
<td>Number of patients with next interval determined as &gt;12 weeks</td>
<td>63 (56.8%)</td>
<td>67 (57.8%)</td>
</tr>
<tr>
<td>Number of patients with next interval determined as 16 weeks</td>
<td>39 (35.1%)</td>
<td>47 (40.5%)</td>
</tr>
</tbody>
</table>
ranibizumab. Their study protocol extended patients out by 2 weeks at a time, with a maximum of a 12-week treatment interval. The study showed that TAE dosing with ranibizumab was non-inferior \( (P < 0.001) \) and had clinically comparable results in visual acuity (6.2 letters vs. 8.1 letters, respectively) compared to monthly dosing after 52 weeks.

The TREX-AMD study is a prospective study comparing patients treated with monthly dosing versus those treated with TAE protocol. This study used an extension interval of 2 weeks after 3 monthly loading doses of ranibizumab, with a maximum extension interval of 12 weeks. Of the patients in the TAE protocol \( (n = 40) \), 68% of patients began interval extension after their mandatory injections or within 1 visit, while 10% of patients were never able to be extended. Their 1-year results showed patients on the monthly regimen gained an average of 9.2 letters while the patients on the TAE protocol gained an average of 10.5 letters, though the difference was not statistically significant \( (P = 0.60) \). The mean maximum extension for patients on the TAE protocol was 8.4 weeks after the first 3 monthly doses.

### Retrospective studies with TAE arm

A retrospective study performed in Paris by Oubraham et al. compared a PRN protocol \( (n = 52) \) versus TAE protocol \( (n = 38) \) with ranibizumab. The results favored the TAE group as there was a significant difference in gain of letters \( (10.8 \text{ letters for TAE vs. 2.3 letters for PRN}) \). Although more injections were needed \( (7.8 \text{ for TAE vs. 5.2 for PRN}) \), the TAE group had superior visual outcomes compared to the PRN group.

The UK AMD/DR EMR Report I retrospectively compared outcomes using the national electronic medical record from 21 United Kingdom hospitals of 1884 eyes between ranibizumab given PRN and aflibercept given either with fixed or TAE protocols over 12 months. Aflibercept achieved greater gains in visual acuity at 1 year compared to ranibizumab though the observed changes were relatively small \( (4.1 \text{ letter difference}) \). However, it was suggested that the increased gain in letters in the aflibercept cohort was due to greater frequency of treatment \( (7 \text{ aflibercept injections vs. 5.8 ranibizumab injections}) \) despite a decreased number of visits \( (9.0 \text{ visits in the aflibercept cohort and 10.8 visits in the ranibizumab cohort}) \). The results of the aflibercept cohort in this study are comparable to the results of ALTAIR. This study also raises the possibility that ranibizumab could be given with fixed or TAE protocols to achieve similar visual outcomes.

### DISCUSSION

In comparison to these studies, the ALTAIR study is the first to critically compare different TAE protocols and showed that both the 2- and 4-week extension protocols for TAE regimens improved visual and anatomical outcomes through week 52. The majority of patients in both the 2- and 4-week extension groups of ALTAIR achieved >12 week extension intervals for their anti-VEGF injections. Zero patients in the 2-week extension group were extended to 16 weeks; it is important to recognize that patients in the 2-week extension arm, in comparison to the 4-week extension arm, were unable to be fully extended to a 16-week treatment interval within the 52-week period due to the protocol guidelines of extending only 2-week periods at a time. Overall, these findings demonstrate the efficacy of TAE regimens with both 2- and 4-week adjustment periods, though perhaps a 4-week extension interval is more preferable as it requires less injection and clinic burden to the patient. ALTAIR is the first large prospective randomized controlled study for nvAMD to evaluate two separate TAE regimens using aflibercept.

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**Table 2: Summarized results of studies with TAE arm**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients in TAE arm</th>
<th>Study design</th>
<th>VA gain at 52 weeks (letters)</th>
<th>Mean number of injections at 52 weeks</th>
<th>% of patients extending &gt;8 weeks</th>
<th>% of patients extending &gt;12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALTAIR 2-week arm</td>
<td>255</td>
<td>Prospective</td>
<td>9</td>
<td>7.2</td>
<td>58.50</td>
<td>42.30</td>
</tr>
<tr>
<td>ALTAIR 4-week arm</td>
<td>8.4</td>
<td>Prospective</td>
<td>10.5</td>
<td>6.5</td>
<td>75</td>
<td>38</td>
</tr>
<tr>
<td>ATLAS</td>
<td>31</td>
<td>Prospective</td>
<td>7.9</td>
<td>8.9</td>
<td>41.30</td>
<td>25.10</td>
</tr>
<tr>
<td>LUCAS</td>
<td>432</td>
<td>Prospective</td>
<td>8.2</td>
<td>8</td>
<td>52.40</td>
<td>37.10</td>
</tr>
<tr>
<td>Bevacizumab arm</td>
<td>320</td>
<td>Prospective</td>
<td>10.5</td>
<td>10.1</td>
<td>45</td>
<td>26 (extended&gt;11 weeks)</td>
</tr>
<tr>
<td>Ranibizumab arm</td>
<td>38</td>
<td>Retrospective</td>
<td>10.5</td>
<td>7.8</td>
<td>Not recorded</td>
<td>Not recorded</td>
</tr>
<tr>
<td>TREX-AMD</td>
<td>942</td>
<td>Retrospective</td>
<td>6.1</td>
<td>7</td>
<td>Not recorded</td>
<td>Not recorded</td>
</tr>
</tbody>
</table>

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**DISCUSSION**

In comparison to these studies, the ALTAIR study is the first to critically compare different TAE protocols and showed that both the 2- and 4-week extension protocols for TAE regimens improved visual and anatomical outcomes through week 52. The majority of patients in both the 2- and 4-week extension groups of ALTAIR achieved >12 week extension intervals for their anti-VEGF injections. Zero patients in the 2-week extension group were extended to 16 weeks; it is important to recognize that patients in the 2-week extension arm, in comparison to the 4-week extension arm, were unable to be fully extended to a 16-week treatment interval within the 52-week period due to the protocol guidelines of extending only 2-week periods at a time. Overall, these findings demonstrate the efficacy of TAE regimens with both 2- and 4-week adjustment periods, though perhaps a 4-week extension interval is more preferable as it requires less injection and clinic burden to the patient. ALTAIR is the first large prospective randomized controlled study for nvAMD to evaluate two separate TAE regimens using aflibercept.
Some drawbacks to the ALTAIR study may include the generalizability of the study. Because this study was carried out in the Japanese population, it may include a higher rate of patients with polypoidal choroidal vasculopathy than when compared to other populations.[22] Furthermore, ALTAIR’s study protocol had a maximum treatment extension interval of 16 weeks; treatment interval extension beyond 12 weeks is relatively uncommon in other trials, and it may be difficult to compare this trial to other clinical studies. Further analysis of disease activity with fluorescein angiography or optical coherence tomography angiography at various time points may provide more data and allow investigators to determine why particular patients are able to be extended out further than other patients based on a patient’s baseline demographics.

Overall, there is a lack of long-term assessments of patients with TAE regimens. In light of studies demonstrating loss of vision after the initial visual gains 5–7 years from treatment initiation,[23,24] it would also be important to confirm that TAE regimens do not perform in the same fashion. Other drawbacks to TAE regimens include the degree of variability for fluid recurrences and how TAE protocols can differ for how patients’ treatment intervals were extended or shortened.[18,19]

CONCLUSIONS

TAE is a useful dosing strategy for nvAMD given the variable nature of the disease and the range of responses that patients have to VEGF suppression. There has been some disparity between results in visual outcomes observed in randomized controlled trials and those of routine clinical practice. The dosing interval in TAE can be carefully adjusted based on a patient’s functional status and their anatomical conditions within the disease progression. For providers, TAE may be a preferred dosing regimen for nvAMD compared to other dosing regimens such as PRN and fixed dosing.

TAE protocol allows for an individualized therapy that avoids both under- and over-treatment for patients. As evidenced in the ALTAIR study, an interval extension of 4 weeks may be sufficient to monitor treatments. This allows for less burden for patients as well as cost effectiveness. Unlike the monthly dosing regimens, a major benefit to the TAE protocol is that it identifies patients who do not need continuous monitoring and ongoing injections. In addition, unlike PRN regimens, TAE can minimize setbacks and recurrences of fluids while maximizing long-term visual outcomes.

ALTAIR and other previous studies examining TAE dosing have consistently showed a gain of about 8–10 letters with the use of anti-VEGF agents as well as an overall reduction in treatment burden and frequency of visits. In routine clinical practice, individualized dosing using TAE protocol with an interval extension of 4 weeks may be sufficient to monitor and treat a patient’s nvAMD disease progression while minimizing the frequency and cost of treatment.

REFERENCES


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