THE GREAT FLUID DEBATE

Reviewing Treatment Outcome Goals for the Wet AMD Patient

Independent medical education supported by Novartis & ZEISS
Baseline Trends in Wet AMD Treatment

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The Great Fluid Debate relates to the management of patients with neovascular age-related macular degeneration (wet AMD). The Interim 2019 EURETINA Clinical Trends Survey was designed to collect information on current practice trends and standard of care in treatment of wet AMD, and to identify unmet needs. It included 33 questions, and almost 300 EURETINA delegates participated in answering the online survey.

Practice Patterns
Practice patterns among the respondents are quite varied as shown by a widespread number of anti-VEGF injections performed in their practices weekly. Importantly, 27% of respondents perform over 30 anti-VEGF injections per week.

Patient Adherence
Patient adherence is key to the success of treatment. Not returning for monitoring or treatment can cause patients to irreversibly lose visual function. When asked what percentage of patients who require regular anti-VEGF injections are adherent with their treatments’ timeframes, 32% reported that less than 60% are adherent. This is an alarming number, so we need to think about strategic approaches moving forward to improve it. Emerging therapies will also help address this issue.

Treatment Approach
Different approaches are used in terms of when to have a patient return for anti-VEGF injections. Some may inject monthly, others use an as needed (PRN) regimen, and others a treat-and-extend approach. There are also hybrid forms combining the latter two. And there may not be uniform definitions on re-treatment criteria.

In answering what the preferred treatment regimen is for patients with wet AMD, there was a split between Western and Eastern Europe. The vast majority of Western European respondents, 85%, preferred a treat-and-extend, or a hybrid PRN/treat-and-extend approach for neovascular AMD treatment. For Eastern Europeans only 59% prefer that same management. There is not enough data to draw conclusions, but it’s possible there are country-specific differences in how ophthalmologists approach their patients. Different reimbursement schemes may also play a role.

Emerging Therapies
Emerging therapies will address compliance and adherence, as well as hopefully improving efficacy. When asked about their level of confidence in understanding the potential impact of emerging AMD therapies on patient outcomes only 44% felt that they are very confident in having ideas of how new emerging therapies differ and distinguish from what is available today.
In clinical practice, it's useful to combine images from all the different modalities and different time points into the same system.”
All Retinal Fluid Should Be Eliminated to Maximise
Outcomes for Wet AMD Patients

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Data from large randomised clinical trials (RCTs) as well as clinical experience show that both SRF and IRF are associated with disease activity. Therefore, intensive intravitreal treatment with anti-VEGF agents is needed to achieve best functional outcomes.

Published Guidelines
This is also reflected by guidelines on the treatment of wet AMD such as the 2014 published EURETINA Guidelines. These guidelines recommend that whenever any evidence of fluid is noted by retinal imaging, an injection should be given to secure the optimal results in vision outcome. In addition, more and more data on long-term outcomes after anti-VEGF treatment has become available, supporting the fact that intensive treatment offers the best outcomes. The image below shows results from a metaanalysis of long term outcomes with different treatment regimens essentially showing that the number of injections correlates with visual acuity gains at five years of treatment.

Type of Fluid Matters
Whereas the negative effects of persisting IRF are undisputed, there is more controversy about persisting SRF or sub-RPE fluid. Almost all studies have shown IRF to be a poor prognostic factor for visual function and that it needs to be treated aggressively until maximum resolution is achieved.

Multiple studies show that stable SRF may be associated with better visual outcomes, but this has only been shown for the first two years of treatment. However, we don’t know what the functional outcome will be if someone has SRF for several years.

OCT Imaging
OCT images of patients with SRF often show that the outer retinal layers are less disrupted than in patients with IRF. However, we do not have data about the effects of persisting SRF over the course of many years. Clinical experience from patients with central serous chorioretinopathy would suggest that this would lead to photoreceptor degeneration in the end.

Questions About SRF
Something to consider is that the presence of SRF may positively influence the need for retreatment, so these patients may potentially get more frequent injections. As these patients receive more injections, they do a lot better and are able to maintain the initial visual acuity gains.

Another thing to remember is that residual SRF may not always represent ongoing neovascular activity. It may instead be dysfunction of the retinal pigment epithelium leading to SRF accumulation, much like central serous chorioretinopathy.

In addition, there are still many open questions such as how much SRF we can tolerate. For example, what would be the exact amount of fluid we can tolerate?
**Conclusions**

Current knowledge from studies, but also from clinical experience, suggests that residual fluid is associated with poorer visual outcomes. The exact role of SRF is still not fully elucidated and needs to be confirmed in further clinical trials. However, as SRF is a sign of persisting activity I would recommend to treat until maximal resolution is achieved. Based on current clinical data and clinical practicability, outcomes are best if all fluid is treated rigorously when using protocols other than fixed dosing, or in other words, “if in doubt, inject the fluid out.”

**References**


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**AMD Patients Can Tolerate a Small Amount of SRF With no Impact on Visual Outcome, and it May Be Helpful in Some Patients**

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The argument of needing to remove all fluid is very extreme. Let’s look at the other side of the argument, using real data.

The Interim 2019 EURETINA Clinical Trends Survey shows the usual mix of responses for fluid threshold goals. Leakage is the hallmark of exudative AMD, but are all fluids the same? And should fluid be handled the same in practice as in testing, which is not the real world?

**Are all Fluids the Same?**

Patients with IRF prior to initial treatment don’t do as well as those who have none. But patients who have SRF at baseline surprisingly do better in what I call the mid-term than patients who do not. This is true regardless of the anti-VEGF agent being used.

So, fluids are not the same, and SRF is correlated or associated with better visual acuity. This is not causality, just correlation: patients with SRF are often type 1 CNV and may have no atrophy, and the SRF involved in the centre of the fovea can cause low visual acuity that can resolve with SRF resorption for example.

**During the Follow-up**

A similar trend is found in patients having SRF during the procedure. Again here, patients who have IRF won’t do as well as patients who don’t. But those who have SRF during the study do better than those who don’t. So, it’s not just at baseline but later on too, again demonstrating the fluids are not the same.

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**What is your fluid threshold for treatment of patients with wet AMD?**

- I accept a small amount of SUBRETINAL or INTRARETINAL fluid, but only if OCT and visual acuity is stable: 35%
- I accept a small amount of INTRARETINAL fluid because I feel it is tolerable or may be beneficial, but subretinal fluid is not acceptable: 3%
- I accept a small amount of SUBRETINAL fluid because I feel it is tolerable or may be beneficial, but I don’t allow intraretinal fluid: 24%
- I accept a small amount of fluid that would not be detected on time-domain OCT: 9%
- I accept no fluid: 29%

The Interim 2019 EURETINA Clinical Trends Survey outcomes: Fluid thresholds. It was found that 71% of delegates do accept small amounts of fluid.

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**The FLUID Study**

The FLUID study looked at the treatment strategy of removing as much fluid as possible. Patients were randomised into the relaxed arm and the intense arm. Both used treat-and-extend regimens with 0.5 mg of ranibizumab. Patients in the relaxed arm were treated until resolution of IRF was achieved, or until there was less than 200 microns of SRF only at the centre of the fovea, and in the intense arm until complete resolution of IRF and SRF was achieved. The results showed that there...
Reconsider Extreme Treatment

If you believe in removing all fluid, look at the CATT study, where a third of patients, and in the FLUID study where 10% of patients even after numerous injections, still had SRF. You can’t just keep injecting more and more. There are other reasons for this occurrence, as flat, irregular, pigment epithelial detachment (FIPED) or SRF at edges of pigment epithelial detachment, etc., and continuing injections in these patients won’t make a difference.

In some cases, injecting too much could harm the CNV. That might seem desirable, but maybe not. In type I CNV there are some data suggesting that in the area of the CNV there is no atrophy, though there is atrophy in other places. The area under the CNV is said to be “protected.” Perhaps this type of CNV has some protective effects that can be nurtured. Similarly to raising children, you don’t let them do whatever they want, at some point you have to say, “a little bit is okay, but too much is not good.”

According to the EURETINA survey, that’s what is mostly done, because doctors have real patients, not theoretical ones. And 71% of respondents sometimes tolerate fluid in their patients, possibly due to treatment burden of a more extreme approach.

Conclusions

Having some SRF does not seem to be as detrimental as having IRF and may even correlate with good results. The protocols tried for extreme treatment to dry up all fluid don’t do significantly better than more relaxed treatment.

Increasing the number of injections can impact the quality of life and treatment adherence of the patient. Some patients will not keep returning if the injections are too much of a burden.

The collective intelligence of doctors in daily practice is on this side of the debate, that a small amount of SRF can sometimes be tolerated in the AMD patient with no impact on their vision. It is only tolerated because doctors are pragmatic and not extremists. A future treatment that gets rid of all fluid without negative effects will be welcome as a solution that can make everyone happy.

References


Recent OCT Fluid Analyses and Their Clinical Implications

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When it’s suggested that some patients do well with some fluid, it’s important to remember that they’re still being treated to try and get the fluid out. Nobody is leaving fluid behind on purpose.

Analysing Fluid That Remains

How can we analyse the fluid that doesn’t dry up? One way is to analyse drugs and how well they eliminate fluid. The OCT is the most important objective biomarker used to decide to switch to a different drug, or determine whether to treat a patient. But how do we use the OCT to compare drugs?

We have historically compared drug A and drug B to determine which drug dries the patient faster. Or we have compared drug A and drug B, and see which drug dries more patients than the other. But those are no longer the only two comparison options.

“...if a physician chooses to accept some fluid, it can be done only under the condition that the patient is continually followed up and treated as needed.”

A New Way of Analysing Fluid

There is a fascinating new method of analysing fluid, which is to compare two drugs and see which causes fewer fluctuations in central subfield thickness (CST), as seen on OCT. This was first done by Dr.
Usha Chakravarthy, who analysed the CATT and IVAN studies. Information gained with this method may be very important. Dr. Chakravarthy’s group divided the patient population into four different quartiles – from those that didn’t have very much fluctuation, up to those that had a lot of fluctuations. It should be emphasised that this was agnostic of the drug, they looked only at the fluctuations.

In a collaboration between physician investigators and Novartis, we then did the same analysis with the HAWK and HARRIER data. Minimal fluctuations were used as the reference point. With fluctuations considered a dose, it was clearly seen, in a dose-dependent fashion, that the more fluctuations there are, the worse the vision. It’s remarkable and absolutely consistent in all studies.

Confidence in the Method
When dose-dependent consistency is seen, it provides a lot of confidence. What provides even more confidence is that the results of this study look virtually identical to what the previous group showed with the CATT and IVAN data. We now have four studies done by two different groups that all show fluctuations in CST may be a new and very important way to look at OCT data, in terms of how it will impact vision.

Early Prediction
Very importantly, looking at fluctuations and separating them into quartiles to predict how a patient is going to do can be done as early as week eight. When following change in BCVA over time, separation was seen in the response of the quartiles at week eight, and the resulting plot lines never crossed through the end of follow-up.

Thus, at that early point it will be possible to tell a patient they may need more injections with closer follow up because their fluctuations are greater and to tell another patient they may be able to have a slightly relaxed treatment regimen because their fluctuations are less.

Combine the Data
Fluctuations in CST are not in opposition with seeing fluid on OCT. The two go hand-in-hand. Separating the quartiles and looking at who had fluid, we saw that patients with more fluctuations also were more likely to have fluid, which makes sense. They were more difficult to treat. So there is a direct correlation between vision, fluid, the amount of fluid, and fluctuations in CST.

Conclusions
There are different ways to look at OCT data, and different analyses are being done to compare drugs, because it’s important to have objective data. The objective data can include how quickly a drug dries the retina and also in how many patients it is effective for drying the retina. But a new third method, which may be equally or more impactful, is to look at what effect a drug has on fluctuations in CST, which may prove to be extremely meaningful for these patients.

References
1. Evans RN, Chakravarthy U, Reeves B. Associations between variation in retinal thickness and visual function. ARVO 2019 poster #3456.

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Some Stable SRF May Be Acceptable

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Prior to the “Great Fluid Debate” symposium, the audience response system (ARS) answers for fluid threshold in patients with wet AMD showed only 28% of respondents answered that a small amount of SRF is acceptable, but not IRF. This is surprising, because, while there is still a debate of whether or not SRF is important, there’s almost a consensus that IRF is worse than SRF. I was also surprised that 7% accept small amounts of fluid on time-domain OCT, simply because I wouldn’t think time-domain OCT would be used anymore. So even though 7% is not a lot, it’s surprising that some still use this method. For the respondents thinking SRF is worse than IRF, 8% may seem like a small number, but it’s larger than it should be, as this is not the common belief. And almost a third of respondents said they accept a small amount of fluid if it remains stable, and if visual acuity is also stable, which is a widely held view.

With regard to SRF, some believe the retina should be completely dry, and may move a patient to a drug they believe will make the retina drier, for example choosing brolucizumab over aflibercept based on trial results. Others think it’s not necessary to continue treatment as long as visual acuity and fluid levels remain stable.

Very importantly, if a physician chooses to accept some fluid, it can be done only under the condition that the patient is continually followed up and treated as needed.

As I would expect, about two-thirds of respondents were very confident in their ability to diagnose wet AMD using multimodal imaging and then a little more after the symposium based on what they had learned. It makes sense that 20% to 30% would be only somewhat confident even after the symposium, because the process allows variability of interpretation, so they may not have complete confidence in the process. Physicians don’t always diagnose the same as reading centres, or even the same as other physicians. This includes detecting activity of disease as well as existing AMD. And almost everyone plans on using multimodal imaging, which certainly is better than using a single imaging mode.

Following the programme, almost all respondents emphasise that IRF is more dangerous than SRF. About two-thirds thought so at first, and almost everyone after reflecting what was said in the programme.

Everyone wants to reduce fluid. The debate is, if you can’t reduce it, and visual acuity is not declining, and the degree of

What is your fluid threshold for treatment of patients with wet AMD?

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<tr>
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<th>Pre</th>
<th>Post</th>
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<tbody>
<tr>
<td>I accept no fluid</td>
<td>25%</td>
<td></td>
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<tr>
<td>I accept a small amount of fluid if it’s not detectable on time-domain OCT</td>
<td>7%</td>
<td></td>
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<tr>
<td>I accept a small amount of SUBRETINAL fluid, but I don’t allow intraretinal fluid</td>
<td>28%</td>
<td></td>
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<tr>
<td>I accept a small amount of INTRARETINAL fluid, but I don’t allow subretinal fluid</td>
<td>8%</td>
<td></td>
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<tr>
<td>I accept a small amount of SUBRETINAL or INTRARETINAL fluid, if OCT and visual acuity is stable</td>
<td>32%</td>
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Based on what you have learned today, which type of retinal fluid do you consider having the most negative impact on visual outcomes in patients with wet AMD?

<table>
<thead>
<tr>
<th>Fluid Type</th>
<th>Pre</th>
<th>Post</th>
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<tbody>
<tr>
<td>Subretinal fluid</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Sub-RPE fluid</td>
<td>6%</td>
<td></td>
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<tr>
<td>Intraretinal fluid</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>Choroidal fluid</td>
<td>4%</td>
<td>94%</td>
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SRF is stable, do you just observe, or perhaps look at another drug? If a patient is stable without treatment, the decision to choose only observation can reduce patient burden, side-effects, and cost. Of respondents in the survey, two-thirds continue to try to reduce fluid level to improve BCVA, and a third still believe that’s not necessary. I think even for those in that group it’s only true if visual acuity is stable and retinal fluid is not increasing and only with the patient being continuously followed up, and treated as necessary.