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An Update for patients on new treatments and trials for cardiac ATTR amyloidosis at the UK National Amyloidosis Centre (NAC)

This information is relevant for patients attending the National Amyloidosis Centre who have cardiac ATTR amyloidosis. New treatments are likely to be available for treating cardiac ATTR amyloidosis in the near future. This letter is to update patients about access to these new treatments.

Background

Cardiac ATTR amyloidosis is caused when the blood protein transthyretin (TTR) collects in an abnormal form as amyloid deposits in the heart muscle. Work by pharmaceutical companies has sought to find drugs (medicines) that stop TTR from forming amyloid deposits, either by:

- stabilising the protein (referred to as TTR stabilisers), or
- reducing the amount of TTR the body produces (referred to as TTR-lowering drugs).

Several different drugs are being looked at, with the hope that one or more of them may be able to stop amyloid build-up in the heart, and enable the gradual recovery of patients with hereditary and non-hereditary (wild-type) cardiac ATTR amyloidosis.

Potential New Drugs

Tafamidis early access scheme

A recent clinical trial of a TTR-stabilising drug called tafamidis has shown a good safety profile and some patient benefit. Over a 30-month trial, patients who were taking the active drug, tafamidis, worsened at a slower rate than those who were taking the placebo (dummy drug). In other words, the rate of deterioration slowed, but the disease continued to worsen. During the first 24 months of the trial, those who were taking tafamidis did not live longer than those who were taking the placebo. However, in those who survived more than 24 months, patients on tafamidis did appear to live longer than those taking placebo. This medicine is not yet available to the NHS but approval for its use is currently being sought via the drug regulatory authorities. Pfizer (the manufacturer) has set up an early access to...
medicines scheme (EAMS), like a ‘compassionate-use programme’ to enable patients who meet certain eligibility criteria to be treated with tafamidis whilst the review process is ongoing. A small number of patients will be able to access tafamidis under this EAMS in the UK (130 in the first instance but the number may be increased at a later date). There is no placebo in the tafamidis EAMS, i.e. all patients will be given the active drug.

**AG10 clinical trial**

Another TTR stabiliser drug under investigation is codenamed AG10, produced by a company called Eidos. Laboratory studies show that AG10 is an excellent stabiliser of transthyretin, but this medicine is at an earlier stage of development than tafamidis, and only now entering a phase 3 clinical trial (currently available at NAC). In this trial, two-thirds of patients receive AG10 and one-third receive a placebo; this is called a double-blind randomisation meaning that neither the patient nor the staff at the NAC will know who is on the active drug. After 1 year on the trial, all patients would be able to receive tafamidis too (if it is available in the NHS by then). After the end of the trial (after 30 months) all participants will be given the active drug, AG10 as part of an extension study. If the trial is successful it is still likely to be some years before AG10 could become available in the NHS generally.

**Patisiran or inotersen clinical trials**

Patisiran and inotersen are two TTR-lowering drugs which are now available on the NHS for the treatment of those with hereditary ATTR amyloidosis and who have nerve disease (neuropathy) as the main problem. The companies who make these two drugs (Alnylam and Akcea/Ionis, respectively) are now putting these drugs through clinical trials to test their benefit in patients with cardiac ATTR amyloidosis as their main problem. Again, there are certain eligibility criteria which patients will have to meet before taking part in these two trials. These trials are not open yet at the NAC, but are expected to open soon.

It is important to understand that the risks and benefits in cardiac ATTR amyloidosis of all the drugs mentioned here have not yet been formally accepted and approved by the UK regulatory authorities.

**Summary**

We can now offer patients with cardiac ATTR amyloidosis, subject to various eligibility criteria demanded by the pharmaceutical companies, the opportunity to be treated with tafamidis or to participate in a clinical trial of AG10.

In both cases, patients would need to attend the NAC every 3 months for various simple checks. Given that we know of more than 1200 patients who are eligible to receive tafamidis, we felt the fairest thing would be to use a computer to randomly select patients to be offered the tafamidis EAMS. After starting 20 patients on tafamidis initially, we plan to repeat this randomisation procedure (and will do so after each group of 20 patients has been started on tafamidis), so as to be fair to newly diagnosed patients (we anticipate randomising roughly every 2 months, i.e., next randomisation expected in November 2019).

Possible outcomes with respect to the above are listed below (and are also summarised in Figure 1 on page 3):

1. **You were randomly allocated to be offered tafamidis:** we will contact you within the next two months to ask if you are interested.
2. **You were randomly allocated to be offered tafamidis and are also potentially eligible for participation in the Phase 3 clinical trial of AG10:** we will contact you within the next two months to discuss these options more thoroughly and offer you either tafamidis EAMS or the AG10 trial.
3. **You were not allocated to receive tafamidis, but are potentially eligible for participation in the Phase 3 clinical trial of AG10:** we will discuss this with you at your next NAC appointment and may offer you participation in the AG10 trial.
4. **You were not allocated to receive tafamidis, and are unfortunately ineligible on clinical grounds for the Phase 3 clinical trial of AG10:** for the time being, we are obliged to continue with supportive management (i.e. standard heart failure medicines) alone but you will be included in the next randomisation unless you ask not to be. Alternatively, there are a small number of other hospitals around the country taking part in the tafamidis EAMS and we may be able to refer you to a hospital closer to you for consideration of tafamidis treatment.
It is important to understand that no patient is obliged to accept any treatment that they do not wish to be given. All patients who are offered one of these drugs/trials will have an opportunity to discuss exactly what is involved before needing to decide anything.

Please know that the team at NAC continue to work with the relevant drug companies and NHS authorities to try to allow wider access for patients to these promising novel treatments for ATTR amyloidosis.

There is nothing for you to do after reading this information. The NAC team will contact you directly if you are randomly allocated to receive tafamidis and will offer you trial participation at your next NAC appointment if you are eligible.

The NAC ATTR amyloidosis Team