VEDS Research Update

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Established and emerging medical strategies for the prevention of cardiovascular events in Vascular Ehlers-Danlos syndrome (VEDS)

Simply put, there are no current medical therapies to prevent cardiovascular events in VEDS that have been sufficiently tested through randomized controlled clinical trials to achieve regulatory approval for that indication anywhere in the world. The lack of controlled trials is not an unusual situation for rare disorders and does not preclude consideration of treatment opportunities that are approved for other conditions. This arises when drugs may be thought to hold promise for VEDS based on expert opinion, basic science advances, animal model work, preliminary clinical observations, and/or experience with related disorders. Some recent advances in VEDS research that have been discussed at patient meetings or advocacy group-sponsored webinars have generated a lot of interest, questions, and discussions on this topic. In this light, leadership at the VEDS Movement and The Marfan Foundation thought it would be beneficial to summarize some of this work.

Medications that are in current common use for vascular protection in VEDS:

Based on some success in people with Marfan syndrome, two classes of antihypertensive medications are currently used to try to reduce the risk of arterial aneurysm development, dissection, and rupture in people with VEDS – beta-blockers (b-blockers) and angiotensin receptor blockers (ARBs). Both can lower blood pressure and may act to reduce the stress acting on a weakened arterial wall. b-blockers also reduce heart rate, which could also reduce arterial wall stress. ARBs appear to afford protection by suppressing a set of signaling events induced by abnormal fibrillin-1 proteins produced by cells in the arterial wall. Most of the work that supported the use of these agents was done in mouse models of Marfan syndrome (MFS) and then supported by clinical trials in people with MFS. The genetic causes of VEDS and MFS are different—Marfan syndrome results from mutations in *FBN1,* and VEDS results from mutations in *COL3A1*. Because the mechanisms of vascular damage in the two conditions are not the same, it is not clear that lessons learned for one can be generalized to the other. Combined ("meta") analyses of multiple controlled clinical trials have shown that both ARBs and b-blockers afford protection from aneurysm growth and vascular events in MFS[1], and the combination might afford greater protection than either individual therapy. While these treatments have not yet received regulatory (e.g. FDA) approval for MFS, the use of these medications has been widely adopted and advocated in influential and critically vetted professional society guidelines. These medications are widely available and can be prescribed "off-label" in most areas of the world.

Celiprolol is a somewhat specialized b-blocker that combines the activity of more conventional b-blockers (described above) with some proposed potentially beneficial properties regarding tissue penetration and activities. While some clinical studies suggested that celiprolol might be beneficial for people with VEDS[2,3], these studies proved somewhat controversial based on size and study design and were not deemed to be sufficient for regulatory approval by the FDA in the US. Celiprolol is available in Europe for the treatment of hypertension and can therefore be prescribed off-label for VEDS. It is not available for any indication in the USA. Zevra Therapeutics is sponsoring a clinical trial of celiprolol for VEDS in the USA.

Outcomes-based studies for both ARBs and b-blockers have been reported in mouse models of VEDS in the Dietz laboratory at Johns Hopkins in the USA, and the laboratory of Professor Jeunemaitre in Paris, France. Both centers found no evidence that conventional b-blockers protected from vascular events and premature death[4,5]. The Paris group found no evidence that celiprolol afforded protection[5], while the Dietz group found that celiprolol accelerated vascular events and premature death in 2 different mouse models of VEDS[4]. While the Hopkins group did not see evidence for protection with ARBs, the Paris group reported a beneficial effect of ARBs in their model of VEDS[5].

Notably, both conventional b-blockers and ARBs have been demonstrated to be generally safe and well-tolerated in all age groups.

Previously reported experimental agents for the treatment of VEDS:

The Hopkins laboratory found excessive activation of the PKC and ERK signaling pathways in their mouse models of VEDS[3]. Notably, inhibitors of either pathway increased life span in VEDS mice. While ERK inhibitors are available for clinical use, largely in aggressive cancers, the toxicity profile is significant, and access is appropriately restricted. While PKC inhibitors (e.g. enzastaurin) are not currently clinically available, the toxicity profile in people has been determined to be favorable and AYTU Biopharma has achieved regulatory approval to move forward with a clinical trial for VEDS.

Hydralazine is an FDA-approved antihypertensive agent that suppressed PKC and ERK activation and protected the VEDS mouse from vascular events in the Hopkins laboratory, increasing it's life span[4]. The Paris group also saw a suggestive signal for protection, but the study was not sufficiently powered to achieve statistical significance[5]. Hydralazine is a somewhat complicated drug to use as the oral form is generally given four times per day, and close monitoring is needed for potential autoimmune side effects. These data are derived from clinical use to control hypertension. It is not clear how dosing in VEDS would be assessed as hypertension is rarely the issue.

Notably, both the Hopkins group and the Paris group found evidence that a class of blood pressure medications called calcium channel blockers (CCBs) caused earlier

aortic rupture in mouse models of VEDS compared to controls[4,5]. The Hopkins group had previously reported that CCBs accelerated vascular disease in both people and mice with MFS and have since found similar evidence for a related disorder called Loeys-Dietz syndrome. CCBs should be used with caution in these conditions, and only when there is no good alternative for the management of severe hypertension.

New research regarding male sex hormones and VEDS from the Hopkins Laboratory:

The Hopkins laboratory has dedicated substantial effort to try to understand the predisposition for vascular events that is seen in young men with vascular Ehlers-Danlos syndrome (VEDS) during puberty. Their work has focused on a mouse model of VEDS (i.e. “VEDS mice”) that was created using genetic engineering. VEDS mice carry a DNA change (mutation) in one copy of the gene that encodes type III collagen that was previously observed in people with VEDS and is representative of the most common class of mutation in VEDS patients (i.e. a substitution for glycine in the triple helical domain). Left untreated, these VEDS mice show the vascular manifestations of VEDS that include arterial tear, rupture, and premature death as a result of arterial rupture. Compared to female mice with the same genetic alteration, male VEDS mice begin to have vascular events earlier in life than the females, at the onset of puberty (~35 days of age in mice). By the end of puberty (~60 days), survival is 48% in males and 66% in female VEDS mice.

Male sex hormones (called androgens) surge with the onset of puberty and are important for the development of normal male secondary sexual characteristics. Androgens are also present in females, but at low levels. Based on these observations, the Hopkins laboratory proposed testing the hypothesis that androgens contributed to accelerated vascular disease in male VEDS mice. VEDS mice were treated with a drug called bicalutamide (an androgen receptor inhibitor or ARi) that prevents the ability of androgens to stimulate cells throughout the body by blocking the receptor for androgens that sits at the cell surface. When initiated at weaning (day of age 21 in mice), the use of an ARi increased survival at day 60 from 48% to 70% in male VEDS mice[4]. A comparable level of protection (81% survival at 60 days) was seen in male VEDS mice upon targeted disruption of the gene encoding the androgen receptor[4]. Neither pharmacologic nor genetic inhibition of androgen activity afforded significant protection in female VEDS mice, but they already had longer complication free survival.

In recognition that use of a potent ARi would lead to significant alterations in sexual development, most prominently in males, we looked for drugs that might modulate androgen-mediated events in VEDS. One possibility was a widely used diuretic called spironolactone that works by blocking both the AR and a different receptor called the mineralocorticoid receptor (MR). Spironolactone is used to treat many androgen-related medical conditions in women including androgenic acne or hair loss and masculinizing effects of polycystic ovarian disease. Spironolactone can cause feminizing effects in a subset of men such as breast tissue development or erectile dysfunction but this is reversible upon drug cessation. The MR responds to chemicals in the body called mineralocorticoids such as aldosterone or glucocorticoids such as cortisol. One of the

major functions of the MR is to regulate salt and water balance through actions in the kidney. MR inhibitors (MRi) such as eplerenone or finerenone are used to lower blood pressure or treat heart failure.

Initiation of treatment with spironolactone vs. placebo at weaning resulted in near-complete survival of VEDS mice through puberty in both sexes (transition of survival at day 60 from 66% to 96% in females and from 49% to 88% in males)[4]. Initiation of spironolactone after puberty (day 60) achieved essentially-complete (>95%) survival of VEDS mice of both sexes into later adulthood (day 100)[4].

Because spironolactone (which blocks both the AR and MR) appeared to have a better performance than selective AR inhibition with bicalutamide or genetic manipulations, we reasoned that the MR was likely contributing to vascular disease predisposition in VEDS and that MR blockade might be beneficial. To test this, the Hopkins laboratory treated VEDS mice with the selective MR inhibitors eplerenone or finerenone, the latter being somewhat more potent. Eplerenone started at weaning resulted in intermediate protection in male VEDS mice at 60 days of age (73% survival vs. 49% in the untreated and 88% in the spironolactone treated animals). Preliminary data with finerenone suggested an intermediate survival benefit in VEDS mice of both sexes[6].

Summary of Mouse Model Treatments

1. Currently available agents with a definitive efficacy signal in people with VEDS:
   - None
2. Currently available agents with a strong efficacy signal in mouse models of VEDS and (at least) a tolerable safety signal in (at least) some contexts:
   - Spironolactone[A,B,C] - well tolerated in females
   - Mineralocorticoid receptor inhibitors[3] (e.g. finerenone, eplerenone) – well tolerated in both sexes
   - Hydralazine[A]
3. Currently available agents with a strong efficacy signal in mouse models of VEDS but a strong safety concern:
   - ERK inhibitors[D] (e.g. erlotinib, cobimetinib)
   - Androgen receptor inhibitors[2] (e.g. bicalutamide)
4. Currently available agents with a mixed efficacy signal in mouse models of VEDS but no strong deleterious safety signal:
   - ARBs[A,C] (e.g. losartan, irbesartan)
5. Currently available agents with no efficacy signal in mouse models of VEDS but no strong deleterious safety signal:
   - Conventional b-blockers[A] (e.g. atenolol, metoprolol)
6. Currently available agents (in at least some markets) with no efficacy signal in mouse models of VEDS and a strong safety concern in at least some contexts:
   - Celiprolol[A]
   - CCBs[A] (e.g. amlodipine, verapamil)
7. Experimental agents with a strong efficacy signal in mouse models of VEDS and no strong deleterious safety signal:

- PKC inhibitors (e.g. enzastaurin)

Special Safety Considerations:

[A]Antihypertensive agent. Can cause low blood pressure. Special care and monitoring when used in combination.

[B]Androgen receptor inhibitor. Risk of altered male sexual development and function.

[C]Can cause high potassium. Special care and monitoring when used in combination.

[D]Risk of retinal detachment – a baseline risk in VEDS.

Some final thoughts:

There are many options worthy of consideration and discussion. Prior to, through and after puberty, spironolactone for women and mineralocorticoid receptor inhibitors for men seem promising based on animal model data. Hydralazine had less of a protective effect during puberty, but was effective in both sexes thereafter. Consider participation in the celiprolol or enzastaurin trials, when they become available, but make sure that the situation is carefully monitored. ARBs seem to be the most validated "conventional" option for aneurysm conditions. Avoid CCBs, ERK inhibitors and selective androgen receptor inhibitors unless there is a specific requirement and no good alternative. It is important to remember that studies in mice do not always have the same outcome in people.

1. Alex Pitcher et al, Angiotensin receptor blockers and β blockers in Marfan syndrome: an individual patient data meta-analysis of randomised trials. 2022 The Lancet , Vol 400, Issue 10355, P822-831.

2. Ong K-T, Perdu J, De Backer J, et al. Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: a prospective randomized, open, blinded-endpoints trial. Lancet 2010;376:1476–84.

3. Frank M, Adham S, Seigle S, et al. Vascular Ehlers-Danlos syndrome: long-term observational study. J Am Coll Cardiol 2019;73: 1948–57.

4. Bowen, CJ etal Targetable cellular signaling events mediate vascular pathology in vascular Ehlers-Danlos syndrome. J Clin Invest 2020 Feb 3;130(2):686-698.

5. Legrand A, Guery C, Faugeroux J, Fontaine E, Beugnon C, Gianfermi A, et al. 2022 Comparative therapeutic strategies for preventing aortic rupture in a mouse model of vascular Ehlers-Danlos syndrome. PLoS Genet 18(3): e1010059. https://doi.org/10.1371/journal.pgen.1010059

6. Dietz H, et al, unpublished, presented at NAVBO Meeting 2022.