Understanding Emerging Bleeding Disorder Therapies

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- There is a lot of activity and innovation underway today in the area of "emerging therapies," that is, potential treatments that are under investigational study and not yet FDA-approved.

- A reason to continue seeking and developing new bleeding disorder therapies is that there is still room for improvement in managing bleeding disorders. Current factor replacement therapies impose a burden of frequent injections, present the challenge of dealing with rapid peak-to-trough fluctuations in factor levels, require intravenous infusions and their complications (access issues, port infections, etc.), and do not prevent all joint deterioration even when prophylaxis is introduced early.

- Currently emerging therapies can be grouped into five categories: (1) factor concentrates, (2) *in vivo* gene therapy, (3) cell therapy, (4) substitution therapy, and (5) "rebalancing" therapy. The first three involve replacing missing clotting factors, while the last two involve non-factor treatment strategies for clot production.

- New **factor concentrate therapy** products are in the investigational pipeline for Factors VII, VIII, and IX.

- One such investigational product is BIVV001, which uses fragments of three other proteins (vWF, Fc, and XTEN) to stabilize Factor VIII and extend its half-life. Phase 3 clinical trials of the product are currently beginning at multiple sites. Results from a Phase 1/2 trial suggest that BIVV001 has a half-life of about 40 hours and might make it possible for persons with severe hemophilia A to maintain a prophylaxis regimen of infusing only once a week. BIVV001 is also in Phase I trials for use in treating vWD types 3 and 2N.

- Another extended half-life factor concentrate therapy now in Phase 3 trials – marzeptacog alfa, or MarzAA – uses a recombinant activated Factor VII (FVIIa) variant and is administered subcutaneously. Because it involves a different pathway of the clotting cascade from the FVIII/FIX pathway, MarzAA has the potential to be used for hemophilia A or hemophilia B patients with inhibitors. It is also in early phase studies for treating persons with FVII deficiency and Glanzmann Thrombasthenia.

- ***In vivo* gene therapies** for bleeding disorders inject an adeno-associated virus (AAV) into the bloodstream to deliver genetic material to the liver, where the machinery within

hepatocytes (i.e., liver cells) can then manufacture the previously lacking clotting protein. Multiple gene therapies targeting hemophilia A or B are currently being studied in clinical trials.

- Clinical trial data for valoctogene roxaparvovec (Roctavian), a FVIII gene therapy, indicates that the therapy is effective at increasing FVIII levels. Phase 1/2 trial participants experienced high factor levels in the first year after receiving the therapy; factor levels declined gradually over the ensuing years, but the rate of decline slowed, and the average FVIII level was still 24.6% four years after administration. Roctavian also reduced annual bleed rates (ABR). In a Phase 3 trial, 80% of the trial participants had no more bleeds after the first five weeks, and at 72 weeks the average ABR decline for all trial participants was 84%.

- In a trial with 10 participants, a gene therapy for FIX deficiency, SPK-9001, produced a 94.1% ABR reduction. In addition, most of the participants reached FIX levels in the 10-40% range and were maintaining those levels relatively consistently two years after treatment. In an early-stage trial of another FIX gene therapy, AMT-061, the three participants achieved factor levels of 30-50% during the first year. A Phase 3 trial of AMT-061 then enrolled 54 subjects. Their average factor level rose to 37% after six months and were still at that level at 18 months.

- Researchers watch for a variety of safety issues surrounding gene therapies. These could arise in both the short term (for example, thrombosis, liver toxicity, immune responses to the therapy) and longer term (for example, development of other disorders or integration of the delivered gene into a site in the cell's DNA that can lead to tumor formation).

- Lenti-FVIII, a **cell therapy** that is being explored for persons with hemophilia A and inhibitors (and is at the point of recruiting for Phase 1 trials), aims to use a person's blood stem cells and modify them so that the cells that develop from them are able to create and store FVIII. When the modified stem cells are put back into the person's body, they can develop into FVIII-containing platelets in the bone marrow. It is hoped the platelets will then circulate in the blood and, when activated by a bleed, deliver more FVIII directly at the site of the bleed before inhibitors can destroy the factor.

- Another cell therapy being investigated, SIG-001, uses a different strategy called "encapsulated cell therapy." Cells that have been modified to increase production of a protein – FVIII in this case – are encapsulated in tiny spheres specially designed to protect the cells and minimize becoming coated by the body's fibrosis response. The spheres are then laparoscopically implanted into fatty tissue in a person's abdomen, where they can absorb nutrients and release FVIII. SIG-001 is currently in Phase 1/2 trials.

- Proper blood clotting depends upon a balance between pro-coagulant proteins (clotting factors) and anti-coagulant proteins that break down clots (for example, anti-thrombin, activated Protein C, and tissue factor pathway inhibitor, or TFPI). Instead of achieving hemostasis in hemophilia by adding pro-coagulants (like activated FVII or emicizumab), **rebalancing therapies** aim to promote blood clotting by inhibiting anti-coagulants. Fitusiran and concizumab are two examples of rebalancing therapies that have demonstrated the ability in clinical trials to reduce ABRs significantly when used prophylactically.

- A concern with rebalancing therapies, however, is the risk of thrombosis. The clotting cascade is extremely complex, with many cross-interacting proteins and processes, so interventions at any point must be monitored carefully. Clinical trials on both fitusiran and concizumab were halted after some study participants experienced thrombotic events. Trials have since resumed or are planned to resume for both products.

- Because of the thrombotic risk, the risks and benefits of rebalancing therapies should be carefully considered. These therapies might provide additional prophylaxis options particularly for patients not easily or adequately managed on current therapies (for example, hemophilia B patients with inhibitors). Patients doing well and being effectively managed on other therapies, however, might or might not find rebalancing therapies to be a good fit from a risk-benefit standpoint.

- The expanding portfolio of emerging therapies we are seeing make this an exciting time and increase the possibility of individualizing treatment approaches for persons with hemophilia. Emerging therapies like gene therapy and encapsulated cells also hold potential for being applied to vWD, and clinical trials for use of Hemlibra/emicizumab, a **substitution therapy**, in Type III vWD are currently in the pipeline.

- For all emerging therapies being investigated for bleeding disorders, information about where and what clinical trials are being conducted and which ones are open to enrollment can be obtained through the ClinicalTrials.gov website.