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The future of care for inherited bleeding disorders

Hemophilia Today met with Dr. David Lillicrap, professor in the Department of Pathology and Molecular Medicine at Queen's University, Kingston, Ontario, and associate director of the South Eastern Ontario Regional Inherited Bleeding Disorders Program, to discuss the future of care for inherited bleeding disorders.

We would like to thank Pfizer, not only for their multi-year commitment at the Visionary Level of the CHS BeneFACTORs Club, but also for devoting their sponsor spotlight in Hemophilia Today *to this interview with Dr. David Lillicrap on the future of hemophilia care.*

***Hemophilia Today (HT)**: How would you characterize the current research field for innovative therapies in bleeding disorders?*

Dr. David Lillicrap: Since the early to mid 1980s, when the genes for factors VIII and IX and von Willebrand factor (VWF) were cloned, molecular science has made significant advances in the diagnosis and treatment of inherited bleeding disorders. In many ways, they have become a paradigm for the application of molecular science to improve care, diagnostically and therapeutically. In the last 5 to 10 years, in particular, those efforts have begun to bear fruit. There is incredible excitement for these innovations that will improve the quality of life for patients.

HT: Let's focus first on extended half-life (EHL) factor concentrates which are now available to many Canadians. Please describe them and how they constitute an advance in treatment.

Dr. Lillicrap: One of the limitations with standard clotting factor concentrates given prophylactically is that they have short half-lives. Factor VIII is around 12 hours and factor IX around 24 hours. To maintain therapeutic levels, you need to intravenously infuse these concentrates three or more times a week for hemophilia A and twice a week for hemophilia B. This is a big inconvenience and, in young children, a major practical challenge. Extended half-life products have been bio-engineered to stay longer in circulation and reduce the number of infusions required to maintain good levels of the clotting factors. These products are now licensed and available in many countries. EHL factor IX is a major success story. The products have half-lives 3 to 5 times longer than standard factor IX. This means that you only need to administer these therapies once a week or, in some cases, once every two weeks. Factor VIII has been more of a challenge. The maximum extensions are about 1.8 times longer than the standard of 12 hours. This means that instead of giving factor VIII infusions three times a week, they are given twice a week. The reason for this is that FVIII is carried around the bloodstream

by von Willebrand factor (VWF) and VWF represents a ceiling in terms of extending half-life. Until we deal with that problem, we can't do better.

HT: Beyond the practical aspect of decreasing the number of infusions, how might these products improve health outcomes?

Dr. Lillicrap: There are a number of potential ways. The first is compliance. By giving infusions less frequently, patients can more easily follow their prophylaxis schedules. This will reduce the long-term musculoskeletal damage caused by bleeding. One of the questions with these products, and it's not completely resolved, is this: should we be aiming at trough levels significantly higher than past targets? People are increasingly suggesting that a 1% trough is not enough and that we should be aiming at trough levels around 10% which would eliminate most spontaneous bleeding and protect against most traumatic events in day-to-day living. The EHL factor IX products make this goal very realistic. They have been paradigm-changing and have made a major difference. Long-term outcomes will be much better.

HT: Nevertheless, these are still IV infusions and, especially in children, this is a real practical challenge. Some companies are looking at new ways of delivering replacement therapy, for example, subcutaneously. Could this become a reality in the near future?

Dr. Lillicrap: The two questions usually asked are: one, will there be a pill? The answer at the moment is that there is nothing remotely close to entering the clinic. This is because the proteins are very unstable. Getting through the acid environment of the stomach and intestines makes a pill very difficult. For the foreseeable future, an oral therapy is very unlikely. Second, is subcutaneous administration a possibility? Some of the research companies are testing this. You have to make high concentrations of the proteins. They have to be available in a form that survives subcutaneous administration. And then what is the likelihood of increased inhibitor formation? Fortunately, that appears likely not to be the case. It will be a while before we see subcutaneous factor concentrates in the clinic.

HT: There is a whole range of non-factor products in the research pipeline. How do they work? What are their potential risks?

Dr. Lillicrap: These so-called non-factor therapies are an area of very elegant innovation. There is a lot of excitement in the community about some of these approaches. There are two major approaches which are close to entering the clinic. The first of these is emicizumab, initially developed by Chugai in Japan and now taken up by Genentech in the U.S., and Roche internationally. It is a humanized bi-specific antibody. This means that the antibody binds to two different antigens; one is activated factor IX and the other is factor X, both required to make clotting happen. This antibody in some ways mimics factor VIII. It's an ingenious idea that has taken 15 years to develop. One advantage is that it can be given by subcutaneous injection. So far, it's been given with weekly injections. The half–life is 20 to 25 days and so it could be injected every one to four weeks. The other advantage is that this antibody therapy is not impeded by anti-factor VIII antibodies so it can be given to patients with inhibitors. Moreover, it will probably be effective in patients with factor VIII without inhibitors. The initial trial was in a cohort of 109 hemophilia A patients with inhibitors. Those results were very promising. Bleed rates were very significantly reduced. This is likely to be licensed within a year for adults with inhibitors. There were, however, five serious adverse events in the study, all involving strange types of thrombosis. All involved repeated infusions of high-dose FEIBA (Factor Eight Inhibitor Bypassing Activity) for breakthrough bleeding. This was a drug interaction between emicizumab and FEIBA. This is biologically plausible as FEIBA already contains significant

amounts of activated factor IX and factor X which are the proteins emicizumab uses to drive hemostasis. Because emicizumab is not a clotting factor, we will need to be careful whenever giving procoagulant products at the same times as this antibody. In the inhibitor study, however, there was no evidence of thrombosis when factor VIIa (Niastase) was given for breakthrough bleeds. The thrombotic events only happened with FEIBA. While we need to be cautious, if you speak to the patients and physicians who took part in these studies, they were very happy and saw a huge change in quality of life.

The other way of affecting hemostasis, without replacement therapy with the missing protein, is to re-balance the hemostatic process. If you have a deficiency in of the procoagulant proteins like factors VIII or IX, you can try to promote hemostasis by creating a deficiency in the anti-coagulant mechanism, on the opposite side of the balance. You actually add a second "issue" with hemostasis in addition to the factor deficiencies. The lead therapy is called fitusiran. It prevents the production of antithrombin. By delivering a small nucleic acid molecule to the liver through a sub-cutaneous injection, antithrombin production decreases. If you reduce antithrombin levels down to about 20% of normal, you re-balance the hemostatic equilibrium in hemophilia patients. This is applicable to hemophilia A and B with or without inhibitors and there's no reason to think it wouldn't work in the rare factor deficiencies, like factor X. It's not as clear if it would work in von Willebrand disease as VWF works at the level of the platelets.

Fitusiran is in Phase I/II clinical studies. Phase III studies are planned. In September, however, a patient in the study died of a of a cerebral sinus thrombosis, an intracranial clot. It was treated as a bleed with factor VIII replacement as well as fitusiran. This is a case of one of these unusual agents being given at the same times as a procoagulant, repeated doses of FVIII. The trial has now been put on hold and we don't know what's going to happen. This highlights the unknowns when interfering with hemostasis in ways we haven't done before. We need to be cautious and learn lessons as we go. Does this mean we should not be pursuing these avenues? No, I definitely don't believe that. I honestly believe it would be inappropriate to withdraw but we must be very cautious and learn from these lessons, some of which are very serious. The trials need to be very carefully regulated.

None of this innovation could occur without the generosity of the patients, many of whom will not benefit very much, if at all, from their participation in research.

HT: We've seen stunning advances in gene therapy for hemophilia A and B just in the last year or so. Could you describe these advances?

Dr. Lillicrap: Gene therapy has been coming for 30 years. It is conceptually very easy and practically very difficult. In the last three or four years, however, there's been a major buy-in to gene therapy on the part of biopharmaceutical companies. So instead of this being the domain of academia and small biotech, major companies are getting involved. Currently there are six factor IX gene therapy trials underway and, as of this year, three factor VIII studies. This is dramatically different from five years ago. The factor IX state-of-the–art gene therapy is being developed by a company named Spark. It delivers factor IX levels between 20 and 40 % a year after a single infusion. That's been achievable because they've used a factor IX gene which uses a gain-in-function variant, called factor IX Padua, which has activity 7 times that of regular factor IX; in other words, taking one naturally occurring mutation, over-expression of FIX, and using it to correct another mutation, hemophilia B, which is an under-expression of FIX.

Gene therapy in factor VIII is a harder target. But last year, Biomarin, a biopharmaceutical company, published information that for the first time shows therapeutic levels of factor VIII in seven patients (and now that number is up to 13) ranging from 20% up to 200% of normal

many months after infusion using an adeno-associated virus (AAV) vector. The ceiling for expression of factor VIII of around 5% has now been broken. It's very exciting.

HT: How much longer might it be before children are included as recipients of gene therapy?

Dr. Lillicrap: In hemophilia, there are well-proven therapies so there is no need to rush. What are some of the concerns? First, transient liver inflammation and, second, toxicity to the genome of the recipients. We need to be cautious in using gene therapy in children who have a lifetime risk, albeit a very low risk, of a bad outcome.

HT: Could gene therapy be used in patients with inhibitors?

Dr. Lillicrap: For the group of those who have failed immune tolerance induction, gene therapy would be a very good way to induce tolerance. There's good evidence for this in mice and dogs. But soon of course we will have emicizumab.

One of the things about all this innovation is that there are many effective and safe therapies. This is great for the patient population. But we need to be cautious. It's really, really important for the entire community—patients, families, nurses, physicians—to become as knowledgeable as possible about these new therapies because they work through very different mechanisms. To become informed so as to be able to make a choice from among all these options is critical. It will be challenging for the clinic teams. Understanding how these therapies work, understanding their benefits and risks, matching them with children, adolescents and adults … With all these options, we have an opportunity to really apply personalized medicine but people need to be very well informed.

HT: Looking into your crystal ball, what do you think treatment will look like in 5 years? In 10 years?

Dr. Lillicrap: I think the factor replacement therapies, including both plasma-derived and recombinant, will be with us for at least the next 5 to 10 years. I think in hemophilia A, with and without inhibitors, the arrival of the bi-specific antibody, emicizumab, is a hugely disruptive technology. It could make a massive difference. Treating hemophilia A with a once-a-week or a once-a-month subcutaneous injection? How can that not make a positive change? We'll learn its full potential within the next one to two years. So of all the things that have evolved for hemophilia A, in 5 years I think emicizumab will be the one to make a huge positive benefit. And then gene therapy? It's there and it's working, but it's harder to predict. Some of the limitations are being overcome. Companies like Biomarin say they can make enough vector to treat larger number of patients. But it will take 5 to 10 years to make a big impact. It's an astonishing time. Truly, truly an incredible time for families with hemophilia.

Interview conducted by David Page on behalf of Hemophilia Today.