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Emerging Horizons in Haemophilia Care

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The evolution of haemophilia treatment and care has been fraught with multiple challenges. Significant advances have been witnessed, which are leading to a decrease in morbidity and mortality associated with haemophilia. Starting with plasma, cryoprecipitate, and plasma derived factor concentrates, many other products are now available or in the pipeline. Recombinant factor VIII concentrates make it possible to shift treatment from the management of acute bleeding episodes to one of prevention of bleeding. The major limitation of current replacement is the short half life of factor VIII and IX. In extended half life(EHLs) products, this is extended by adding various moieties, allowing less frequent infusions. Binding of Fc portion of IgG (Fc-fusion technology) and binding of polyethylene glycol (PEGylation) with factor VIII and IX results in decreased clearance and extended half life of these coagulation proteins. These products are well tolerated with less inhibitors to development. Factor VIII extended half life products yielded a modest increase, as compared to factor IX extended half life products. The modest increase in factor VIII half life can be ascribed to the interaction of factor VIII with von Willebrand Factor (vWF) . BIVV,OOL is an EHLs product that includes the D/D3 domain of vWF, which decouples the interaction of F-VIII with vWF, breaking the so called "vWF half-life ceiling," which is responsible for shorter half life.

World-wide, over the standard of care is now prophylactic administration of factor concentrates. Prophylaxis regimens present a beneficial outcome in terms of preventing active bleeds, circumventing joint damage, reducing the risk of inhibitor development, and, as a result, improving overall quality of life. In our part of the world, Chinese and Indian protocols with low dose prophylaxis are yielding acceptable results. These protocols are tailored on the basis of individualized pharmacokinetics, bleeding phenotypes, and an escalation criteria determined by a complementary evaluation system

Therapies that alternate with factor VIII are also designed. A major breakthrough in this regard is bi-specific monoclonal antibody Emicizumab (Hemilibra; ACE910). Emicizumab mimics factor VIII in functions. It binds to factor IX and X, hence leads to thrombin generation, bypassing factor VIII. Emicizumab showed acceptable safety and tolerability profiles given upto a dose of 3 mg/kg/week, subcutaneously. While Emicizumab mimics the functions of factor VIII, it does not resemble factor VIII structurally or immunologically and hence is not liable to produce inhibitors. Emicizumab offers possible solution to unmet needs regarding short half lives requiring frequent administrations, intravenous administration and inhibitors production, seen with routinely administered factor VIII concentrates. It got a half life of approximately 30 days, which avoids the peaks and troughs commonly seen with factor VIII replacement, It can be given once weekly, every 2 weeks or even once per month.

In addition to Emicizumab, other factor VIII mimetics antibodies, like Mim8 and Efanesoctocog alfa, are also under trial. Mim8 claims to bridge factor IXa and Xa in a more potent way, than Emicizumab. Efanesoctocog alfa (BIVV,OOL) is a fusion of a single recombinant factor VIII protein into von Willebrand factor , plus hydrophilic polypeptides to expand the half life of factor VIII.

Haemostatic balance inside the body is delicately poised between procoagulant and anticoagulant mechanisms. Therapeutic agents like Conicizumab, aimed at blocking tissue factor pathway inhibitor (TFPI), Fiturisiran , aimed at blocking antithrombin (AT) and Serin PC , aimed at blocking Protein-C are upcoming options in therapeutic repertoire. All these are designed to tilt the balance towards coagulation, by inhibiting anticoagulant proteins. Inhibition of TFPI, by Concizumab can enhance the haemostatic activity of TF-VIIa and prothrombin complexes. Inhibition of AT, by Fitursiran, is predicted to increase the generation of factor X and thrombin. Serpin PC, inhibitor of Protein-C, is designed to restore levels of prothrombin, which will inturn generate thrombin. Subcutaneous administration and half life of at least two weeks are other benefits of these agents.

In hemophilics, haemophilic arthropathy causes permanent disability. It is important to circumvent this happening. Conservative management, along with factor replacement and prophylactic administration of factor concentrates, are all designed in this regard. But, once chronic arthropathy establishes then interventional strategies are required. Arthroscopic synovectomy, performed under direct vision, can help to visualize proliferated synovium .In this procedure damaged synovium can be removed to maximum extent. Another option in this regard is chemical synovectomy (Synovioarthesis). Intra-articular injections of Rifampacin and Yttrium-90 witnessed more than 80% success rates. Rifampcin, presumably inhibits inflammation and hypertrophy of the synovium, which reduces bleeding episodes and delays progression to joint degeneration and destruction. The total joint physical score, proposed by World Federation of Haemophilia (WFH), significantly reduces after intra-articular Rifampacin and the number of bleeding episodes and pain shows improvement. Now, total knee replacement (TKR) is also recommended in haemophilics with severe orthropathy. For knee replacement, in haemophilics, success rate and long term prosthesis survivorship (10 years) is reported to be more than 85%. It is significant on the face of many complexities and complications, very much inherent in this cohort of patients.

There is a surge for genetic assessment of patients with inherited bleeding disorders. Genetic testing for hemophilics is likely to help in the definition of disease biology, the establishment of difficult cases, the prediction of inhibitor development risk, the identification of female carriers, and the provision of prenatal diagnosis, if necessary.

Haemophilia, being a monogenetic disease, is an excellent candidate for gene therapy. Gene therapy, which aims to induce only a small fraction of normal factor production (a modest goal of about 1 IU/dl), is likely to cure the bleeding phenotype. The most recent trials of gene therapy, in patients with haemophilia, have achieved long term expression of therapeutic factor levels, with a single infusion. The smaller cDNA size of factor IX, as compared to factor VIII , is leading towards more rapid progress in gene therapy in haemophilia B. Attempts are there to address technical problems in the incorporation of cDNA of factor VIII in the vector. Due to non profibility of the BMN 270 (gene therapy of haemophilia A) project, it received an orphan disease status. This trial is likely to offer a possible real, attainable curative treatment option.

World over advocacy of haemophilia cause through bodies like World Federation of Haemophilia, Laurie Kelly Communications and Save One Life (SOL) project and respective haemophilia societies in different countries across the globe are dealing with this problem in an upfront manner. WFH Humanitarian Aid Programme is launched with an objective to respond to the unmet needs for treatment in countries where excess to treatment products is limited or non-existent. The programme helps provide immediate support to patients in need. In Pakistan WFH playing an epic role in easing out the miseries of haemophilics .Low dose prophylaxis and Hemilibra (Emicizumab) pilot projects are in progress, at Haemophilia Patients' Welfare Societies of Pakistan. WFH launched another five years programme in Pakistan under the banner of "Path to Access to Care and Treatment" (PACT). This initiative is designed to improve outreach and diagnosis and increase access to sustainable care for people with inherited bleeding disorders. Laurie Kelly Communications "Save One Live" (S.O.L) project is intended to help people with inherited bleeding disorders to accomplish their educational pursuits. With better availability of treatment, people with inherited bleeding disorders entering in the phase where they

should become a productive component of society and their families. The S.O.L project also assist them to be an entrepreneur, by initiating their independent source of income, in lines with their physical capabilities. Haemophilia Societies try to sensitize philanthropists and the people who matter about this neglected cohort of our society. Other than haemophilia, females with inherited bleeding disorders needs empowerment. HPWSs are playing in important role in this regard. A better coordination between societies and obstetricians are yielding successful pregnancy outcomes in females suffering from von Wilbrand disease, platelet functions defects and other rare autosomal recessive inherited bleeding disorders

With better treatment options now the average age of people with inherited bleeding disorders is witnessing a substantial increase. All this reflects a need to make this cohort a productive component of society. All this needs a comprehensive management plan involving all stake-holders. Patients' empowerment is also required, as patients' motivation and involvement is backbone of all activates. Haemophilics and all those suffering from other inherited bleeding disorders must have the chance to live fully, get education, be a productive component of their representative societies, this unfulfilled dream is very much realizable, and the emerging horizons around the world can be interpreted as the opening of many vistas. All this reflects resilience and perseverance of medical fraternity, societies and wish of the sufferers to accomplish their dreams to the fullest.

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