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Eliminating inhibitors by suppressing targeted cells

Suppression of key cells is likely the best way to eliminate inhibitors in patients being treated for bleeding disorders, according to Jean-Marie Saint-Remy (Belgium). "We have heard a lot about different techniques for identifying patients susceptible to inhibitors and intervening to prevent them, but I think there's little chance this will succeed. It is possible to predict the gene polymorphosis that creates inhibitor susceptibility, but that won't be helpful clinically. Suppression is the more likely practical path to inhibitor elimination."

When normal B-cells develop immunogenicity, it is not that significant because they are very short-lived. However, when memory B-cells are activated into plasmocytes they survive for long periods of time, continuously producing antibody responses. Both *in vitro* and *in vivo* trials (in a transgenic mouse model) have demonstrated that focusing on the specific elimination of memory B-cells through idiotypic interaction is possible, he said. Eliminating these memory cells reduces the number of antibodies produced.

In addition, the presence of specific surface receptors makes memory B-cells extremely easy to activate. This, he suggested, might explain why some hemophilia patients continue to have high inhibitor levels years after their last exposure to FVIII.

It is possible, Saint-Remy said, to use anti-idiotypic antibodies to interfere with B-cell receptor signalling, effectively "shutting off" B-cells leading to apoptosis (cell death). The successful development of a transgenic mouse model means it is possible to more accurately study the most effective interventions and gather important data that could translate this research into practical human therapies relatively quickly.

The induction of adaptive regulatory T-cells might be a complementary approach to inhibitor elimination, he continued. T-cells help B-cells mature by recognizing FVIII-derived or idiotype-derived epitopes. Theoretically, he said, it is possible to interfere with the T-cell arm of the anti-FVIII response. However, there are "legions of T-cells and that makes it difficult to identify which ones react differently in the presence of FVIII," he said. So, even though it's possible to induce reduced B-cell responsiveness or even cell deletion, the huge number of T-cell variables and their "promiscuous" nature make targeting the correct cells a challenge that may prove difficult to surmount.

Still, Saint-Remy concluded, ongoing research will likely make identifying antigen-specific T-cells a reality within five years, providing another opportunity to add to the repertoire of tools to be used against inhibitors.

Yildirim Çelik

Delegates receive therapy at the Treatment Centre, which was generously supported by donations from Baxter, Bayer, BPL (Sodhan), CSL Behring (Farmatek), Erkim Ilac, Grifols, Novo Nordisk, Octapharma, and Wyeth

WFH Award Ceremony Preview

The global bleeding disorders community will honour the outstanding contributions of some of its volunteers, scientists, and twinning partners tomorrow afternoon beginning at 1:00 in Topkapi A.

The WFH Twinning Awards for 2006 and 2007 will be presented to selected treatment centres and patient organizations in recognition of their achievements.

Other prizes that will be awarded include the Vincenzo Pietrogrande and the Henri Horoszowski Awards, presented by the Musculoskeletal Committee, the Inga Marie Nilsson Award, the International Healthcare Volunteer Award, and the International Frank Schnabel Volunteer Award. All delegates are invited to attend the ceremony.

Challenges persist in diagnosing rare bleeding disorders

By and large, rare bleeding disorders are recessive, autosomally inherited conditions that often present difficulties in diagnosis and management. Consequently, it is vital for health professionals – particularly pediatricians – to be educated about the disorders and their symptoms, said Paula Bolton-Maggs (UK).

The lack of clear correlation between factor levels and bleeding tendencies, analytical issues, and interpretation of results make diagnosis difficult. For instance, it is unclear if heterozygotes are truly asymptomatic, since bleeding symptoms have been reported in heterozygous FII, FVII, FX and FXI deficiency. Other difficulties include obtaining good blood samples and pre-analytical factors that require particular care with sampling from infants and children.

There are regional and ethnic variations too, Bolton-Maggs noted, so it is important not to rely on manufacturer package inserts for normal ranges. "Local ranges should be defined using 30 normal adults for all the coagulation factors. A normal APTT does not exclude an intrinsic factor deficiency and pediatric normal ranges are significantly different, which can result in wrong diagnoses."

Internal and external quality assurance are absolutely necessary. They should include standardized operating procedures, reliable reference materials and reagents, appropriately trained staff, and performance checks against other laboratories.

In developing countries, diagnosis of rare bleeding disorders is impeded by numerous issues, said Sukesh Nair (India). Shortages of adequate instruments and reagents, their high cost, and lack of awareness among clinical medical personnel impede diagnosis of rare bleeding disorders, he said.

Moving forward, better methods and systems are needed to obtain accurate results, personnel need better training on methodology and quality assurance, quality control systems must be established, and further laboratory tests and automation developed, depending on resources, he said.

In Latin America, the diagnosis of hemorrhagic disorders depends on economic factors and the availability of qualified personnel, specialized laboratories, and hemophilia care programs, said Arlette Ruiz de Sáez (Venezuela). Resources vary from country to country and sometimes patients have limited access to hemophilia treatment centres.

The presence of strong national patient organizations and development of national patient registries are powerful mechanisms for lobbying for care. WFH programs on patient outreach, laboratory training, and quality assurance have brought improvements to a number of countries in Latin America, she said.

Yildirim Çelik

More than 150 people have already made generous donations in half a dozen currencies to the Count Me In! I Support Treatment for All *donor wall. All funds raised will be used to support WFH programs. It's still possible to make a contribution at the WFH Resource Centre in the Exhibition Hall.*

In the Halls

What knowledge have you gained from this congress and what strategies do you hope to implement in your own community?

I have learned a lot about the scope of medical issues in hemophilia and gained important new knowledge about topics such as inhibitors, gene therapy, von Willebrand disease, and women's bleeding disorders. Hemophilia is considered a male disease but in my view that's not right – it's a carrier disease that affects both men and women. My goal is to return and inform members of my organization about the importance of carrier issues, VWD, and women's bleeding disorders and hopefully incorporate them into our new strategic plan.

– Belgium

My country has limited resources for bleeding disorders, but I have learned a lot about hemophilia, VWD and rare coagulation

Cautious optimism in the treatment of HIV and HCV

Successful advances in human immunodeficiency virus (HIV) and hepatitis C (HCV) treatment, which have vastly improved health outcomes for the general population, are proving equally beneficial to people with hemophilia, according to presenters at yesterday's Infectious Diseases session. But there is still the need for vigilance and care, both in choosing therapies and in promoting transmission prevention.

Estimated rates of infection from HIV and HCV among those being treated with blood-derived products peaked between 40 and 80 percent, Jorge Daruich (Argentina) said, and a significant number are co-infected.

The introduction of highly activated antiretroviral therapies (HAART) in the mid 1990s and ongoing improvements to the drugs and combinations used for the treatment of HIV have significantly reduced morbidity and mortality. "It is at the point where HIV is now just considered a lifelong infection – even for people with hemophilia," he said.

Lucy Dorrell (UK) outlined some of the difficulties encountered in the search for an HIV vaccine. The key to finding one might depend on understanding the small percentage of people who have resistance to HIV-1, possibly on a genetic basis. Noting the significant number of people with hemophilia who were exposed to HIV through blood products but did not develop the disease, she invited participation in the Centre for HIV-AIDS Vaccine Immunology (CHAVI) study, aimed at identifying gene variants that influence susceptibility to HIV-1.

In HCV infection, the introduction of pegylated interferon and ribavarin and more recent studies of liver disease progression have pushed the percentage of favourable outcomes to 72%, with only 28% developing severe symptoms, according to Harvey Alter (US). Still, he cautioned against excessive optimism because of the extremely high levels of infection worldwide.

Making appropriate treatment choices for bleeding disorders patients with both HIV and HCV requires knowing personal history, other co-morbidities, possible drug contraindications, and pharmaceutical complications, Daruich said. In some cases, bleeding disorder therapies diminish the response of other drugs. "That's why it's best to treat these patients with interdisciplinary teams to ensure good therapeutic coordination and the best possible results."

In the Halls

disorders, and the range of treatments available. There is much to be done about diagnosis, prophylaxis and managing inhibitors. The most important task is how to organize people with bleeding disorders to lobby government for more access to treatment products and prophylaxis, and improved access for patients living in rural areas.

– Indonesia

This is my first time at congress and I've found it really worthwhile. Beyond the medical information, the psychosocial sessions were very valuable because it showed that there are other ways to treat the disorder besides factor. At the talk on the psychosocial impact of limits to physical activity and sports, there was a patient with inhibitors who decided to get a pilot's license, and that was very inspiring for me.

– South Africa

Yildirim Çelik

Delegates are already thinking about Buenos Aires in 2010

Sessions to watch for

Plenary 08 Advances in treatment for bleeding disorders have come at a dizzying pace over the past few decades. A summary of those advances and a peek into what the future will likely hold will be the focus of *Back to the Future: A History of the Treatment of Hemophilia.*

Pier Mannucci is presenting, with Paul Giangrande as chair.

Session starts at 9:45 in the Anadolu Auditorium.

D1.1 Hear details of the final report of the International Prophylaxis Study Group, including a report on joint health scores and a proposal for a new international MRI score.

Presenters are Victor Blanchette, Marilyn Manco Johnson, Brian Feldman, Sharon Funk, Bjorn Lundin, and Andrea Doria.

Session begins at 11:00 in the Anadolu Auditorium.

D1.2 From detergent treatment of cryoprecipitate to the prospects of gene therapy treatment - innovations with the potential to improve factor therapies in both developed and developing countries will be discussed at 11:00 in Topkapi A.

Presenters are David Page, Magdy El-Ekiaby, Paul Giangrande, and David Lillicrap.

D2.5 Leading experts will discuss inhibitors, gene therapy, and rare bleeding disorders in the Congress' closing Laboratory Science session. It takes place in Dolmabahce A at 3:00.

Presenters are E.G. Tuddenham, Jorgen Ingerslev, Flora Peyvandi, Simon Waddington, and Erik Berntorp.

Announcements

Farewell Dinner Ticket Holders

Due to the cool evenings that Istanbul is currently experiencing, the farewell dinner has been moved from poolside to the upper level of the Hilton Convention Centre. The cocktail reception will begin at 7:00, followed by dinner at 8:00.

Reminder

Be sure to return your Congress evaluation forms to the Registration Desk for your chance to win a free airline ticket to Hemophilia 2010 in Buenos Aires!

Erratum

In Tuesday's edition, we said that László Kiss had bicycled more than 650 kilometres in his attempt to raise hemophilia awareness. In fact, his journey was 1200 kilometres. We apologize for the error.

Meeting the needs of elderly patients

As treatment advances continue to improve life expectancy for people with hemophilia, meeting the needs of elderly patients requires different approaches, special care, and dedication, Sylvia von Mackensen (Italy) said, in yesterday's session on *How Elderly People with Bleeding Disorders Manage Their Condition.*

The impacts of hemophilia on the health status and physical functioning of elderly patients are considerable, she noted. Medical conditions such as hypertension, viral infections, musculoskeletal problems and increased mobility challenges, along with impairment related to dressing, bathing, transportation, gait, and balance often diminish quality of life as patients age. These changes are frequently accompanied by emotional changes and depression.

Socio-demographic factors also affect elderly people with hemophilia, von Mackensen noted. A recent Italian study of the impact of hemophilia on the everyday lives of elderly patients showed that only 64% of patients are married, compared to 91% in the control group. "This can result in a worse situation because they need assistance but do not have a wife or children to support them. It is really a big problem because they gradually lose autonomy in daily activities."

Els Haan (the Netherlands) described the multidisciplinary care approach for elderly hemophilia patients at the Van Creveld Clinic – established in 1964 as the first comprehensive hemophilia care centre in the world. In the clinic's early years, Dutch patients were unlikely to survive childhood. But today, the availability of clotting factor, prophylactic, antiviral, and home treatment, along with surgical precautions have helped raise life expectancy to 74 years (66 years for those with HIV and HCV).

The clinic has a full complement of staff to manage the needs of elderly patients, including a social worker to help patients cope with psychological consequences of aging, employment issues and family dynamics, a physiotherapist and rehabilitation specialist, infectious disease specialist, urologist, dentist, and hematologist.

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