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HEMATOLOGY
& MEDICINE

ABSTRACT BOOK

7th Interregional Conference of the Reggio Calabria and Catania Hemophilics Associations

OJHM

Editor: G. SOTTILOTTA
Director: D. GRECO MALARA
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Contents

Aims and scope

ONLINE JOURNAL OF HEMATOLOGY AND MEDICINE (OJHM) is an interdisciplinary open access online journal focusing primarily on blood diseases. The journal publishes original contributions in non-malignant and malignant hematological diseases. It also covers all the areas related to the hematological field that takes care of diagnosis and treatment of blood disease. Particular editorial interest is addressed to: Inherited and Acquired Clotting Disorders, Antiphospholipid Syndrome, Clinical Management of Bleeding Diseases, Coagulopathies, Hemophilia, Platelets Disorders, Thrombotic Disorders. Manuscripts should be presented in the form of original articles, editorials, reviews, short communications, or cases report, all submissions are rigorously peer reviewed.

All manuscripts submitted to OJHM must be previously unpublished and may not be considered for publication elsewhere at any time during OJHM's review period.

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Hemophilia A and B, but also other congenital and acquired hemorrhagic pathologies, have known epochal changes in the last few years: the new extended half-life factor VIII and IX concentrates, the imminent gene therapy and the non-replacement haemophilia products are offering medical assistance and a quality of life unimaginable in the past. The challenge for the health professionals who every day deal with coagulopathic patients is the choice of the best product tailored to the characteristics and lifestyle of the patient. The COVID-19 emergency seems to have slowed down the possibility of taking advantage of those innovations. If this is true for industrialized countries like Italy, which still benefit from a satisfying free national health service, for developing countries in the rest of the world, this has impaired the access to care for patients with bleeding disorders. The objective of this 7th interregional conference is also to mark the restart of the scientific and informative activities that have always characterized the spirit of this initiative since its first edition. The topics discussed will concern the new therapies, the impact of COVID-19 on the management of the coagulopathic patient's therapy and also some aspects related to the recent vaccination campaigns. Finally, an ample space will be dedicated to the discussion of orthopedic, physiatric and physiotherapeutic issues. As every year, the aim of this 7th Interregional Conference of the Reggio Calabria and Catania Associations is confirmed: information and scientific updating aimed to health professionals, on the methods of treatment and approach to the various clinical, pharmacological, administrative and social problems. Furthermore, the meeting between the associations of South Italy will increase the relations between their representatives, exchange experiences and improve the management strategies of the doctor-patient relationships, and between patients organizations and health institutions. This determines and affects the management of medical and pharmaceutical care strategies in order to maintain the highest possible attention on rare bleeding pathologies.

Dr. Gianluca Sottilotta **Dr. Gaetano Giuffrida**

Congress Programme

4 DICEMBRE 2021

SESSIONE 1

Moderatori: G. Sottilotta (Reggio Calabria), M. Morfini (Firenze)

8.15	**Saluti iniziali e presentazione del corso** *G. Giuffrida (Catania), G. Sottilotta (Reggio Calabria)*
8.30	**Metodiche nella diagnostica e nel monitoraggio terapeutico delle malattie emorragiche: vecchie e nuove** *R. De Cristofaro (Roma)*
9.00	**Concentrati di Fattore VIII e IX a emivita prolungata: esperienze di «real life»** *E.Zanon (Padova)*
9.30	**Terapia non sostitutiva nel paziente emofilico: presente e futuro** *B. Pollio (Torino)*
10.00	**Il trattamento dell'emofilia nel mondo** *C. Garrido (World Federation of Hemophilia)*
10.30	**Pausa**

SESSIONE 2

Moderatori: G. Giuffrida (Catania), R. De Cristofaro (Roma)

11.00	**Piastrinopenie e piastrinopatie** *Erminia Baldacci (Roma)*
11.30	**La «vaccine-induced immune thrombotic thrombocytopenia» (VITT), la trombocitopenia indotta (ITP) e i report trombotici durante la vaccinazione contro il coronavirus** *P.M. Mannucci (Milano)*
12.00	**Le microangiopatie trombotiche** *F. Peyvandi (Milano)*
12.30	**Il COVID-19 e l'emofilia** *M. Napolitano (Palermo)*

LETTURA SATELLITE a cura di Novo Nordisk (NON accreditata ECM)

Moderatori: G. Sottilotta (Reggio Calabria), M. Morfini (Firenze)

13.00	**Nuovi orizzonti terapeutici in Emofilia B: come ottenere una maggiore protezione per i pazienti** *G. Sottilotta (Reggio Calabria)*
13.30	**Pausa**

Congress Programme

4 DICEMBRE 2021

	LETTURA SATELLITE a cura di Roche
	(NON accreditata ECM)
14.30	**Esperienza in Real Life con Emicizumab**
	G. Giuffrida (Catania)
	Tavola rotonda
	"L'assistenza in ambito muscolo-scheletrico nel periodo COVID e la gestione multimodale del dolore"
	Moderatore: C. Carulli (Firenze)
15.00	**La gestione multidisciplinare del soggetto emorragico nel periodo COVID-19**
	Il parere dell'ortopedico
	C. Carulli (Firenze)
	Il parere del fisiatra
	V. Polimeni (Reggio Calabria)
	Il parere del fisioterapista
	F. Bagnato (Varapodio - RC)
	Discussione
	M. Vecchio (Catania)
15.45	**La gestione multimodale del dolore in emofilia**
	Il punto di vista del terapista del dolore
	M. Consalvo (Roma)
	Il punto di vista del fisiatra
	M. Vecchio (Catania)
	Il punto di vista del fisioterapista
	A. Corsaro (Catania)
	Discussione
	C. Carulli (Firenze)
16.30	**I costi della terapia dell'emofilia nell'era dei prodotti a emivita prolungata e della terapia non sostitutiva**
	P. Cortesi (MIlano)
17.00	**Discussione sui temi della giornata**
	Tutti i relatori
17.30	**Chiusura del Convegno**

Congress Programme

5 DICEMBRE 2021 - NO E.C.M.

9.00	TAVOLA ROTONDA **''I pazienti giovani intervistano i medici''** ***Moderatore**: A. Buzzi* ***Discussants**: P.M. Mannucci, M.Morfini, V. Trapani Lombardo*
9.30	TAVOLA ROTONDA **''I pazienti giovani intervistano i padri dell'associazionismo in emofilia in Italia''** ***Discussants**: A. Buzzi, S. Russo*
10.00	**Pausa**
10.30	**Essere emofilico nel periodo della pandemia: aspetti clinici e psicosociali** *G. Sottilotta, M. F. Mansueto*
11.00	**L'educazione sessuale in emofilia: un bisogno inespresso ?** **Risultati della Survey internazionale** *D. Messina*
11.30	**La storia dell'emofilia attraverso le copertine e gli articoli di EX** *B. Mazzoli*
12.00	**L'emofilia nella storia, cinema, tv e fumetti:** **visita guidata ai cartelloni illustrativi** *S. Frisina*
12.30	**Conclusioni e saluti finali**

Berardino Pollio
Pediatric Hemophilia Center, Regina Margherita Children Hospital of Turin, Turin, (Italy)

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B. Pollio

NON-REPLACEMENT THERAPY IN HEMOPHILIA: PRESENT AND FUTURE

In 2007 Manco Johnson's pivotal randomized trials established that primary prophylaxis is the standard of care for people with hemophilia. In just 15 years, hemophilia has seen an extraordinary development of increasingly innovative molecules. By the end of 2021, an extraordinary therapeutic arsenal of at least a dozen factors designed to reduce immunogenicity and modify clearance in order to increase protection and shorten dosing intervals is available for treatment of hemophilia. The non-factor replacement therapies are novel approaches restoring generation of thrombin by means of monoclonal antibodies mimicking FVIII, antithrombin interference RNA therapy and monoclonal antibodies directed against the tissue factor pathway inhibitor (anti-TFPI). The advent of emicizumab, a subcutaneously administered bispecific humanized monoclonal antibody is a FVIII mimetic, resulting in a dramatic

improvement of quality of patient-life with inhibitors. Moreover, emicizumab is now an alternative form of prophylaxis for patients with severe hemophilia A without inhibitors. The 2021 study of Callaghan et al. demonstrated that 82% of patients treated with emicizumab were free from bleeding during a follow-up of 144 weeks. The real-world data also confirm the efficacy data of the pivotal studies and are reassuring on safety. Hemorrhagic phenotype changes to mild and bleeding episodes are almost exclusively secondary to significant trauma; drug-related thrombotic events remain confined to those of patients enrolled in the first pivotal Haven-1 study and are related to the association with prolonged therapy with FEIBA. Phase III Haven 6 study investigates the efficacy and safety of emicizumab in patients with mild and moderate hemophilia A of any age. Phase III Haven-7 study and the observational study of the Italian association of hemophilia centers (AICE) are under way to collect data on the management of previously untreated patients and children <12 years without inhibitors. Another monoclonal antibody called Mim-8 is a FVIII mimetic under investigation also in children between 1 and 11 years old. Fitusiran is a small interfering RNA (siRNA) that acts by targeting and binding Antithrombin (AT) messenger RNA. It is given subcutaneously and is under investigation in hemophilia A and hemophilia B with and without inhibitors. Patients treated with fitusiran experienced an almost 80% reduction in AT levels. ABR was 1 in patients without inhibitors and 0 in patients with inhibitors. Unfortunately, a Hemophilia A patient suffered a cerebral sinus vein thrombosis following FVIII therapy for breakthrough bleeding that was ultimately fatal. After a clinical hold on the trial, a risk-mitigation strategy was developed and the clinical trial program has restarted. Concizumab and marstacimab are two humanized monoclonal antibodies against TFPI which is a natural inhibitor of extrinsic pathway. Hemostasis rebalancing strategies are particularly interesting because they are potentially useful even in rare disorders of hemostasis. Furthermore, they may represent a valid therapeutic option for the neglected category of patients with factor IX inhibitors. In this amazing scenario of innovative therapies, however, some points remain unchanged regarding the management of patients with hemophilia: the need for careful monitoring of the joint health, the need for adequate adherence to therapy and finally a constant attitude to pharmacovigilance.

Pier Mannuccio Mannucci
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P.M. Mannucci

IMMUNE-MEDIATED HAEMATOLOGICAL COMPLICATIONS AFTER VACCINATION

Haematological complications caused by autoimmune mechanisms which are associated with haemorrhages, thrombosis, or both, have been described after vaccinations against various infectious, viral or bacterial diseases. The most frequent examples occur after vaccines administered to young children (e.g. against measles/mumps/chickenpox/rubella), after vaccination against diphtheria/tetanus/whooping cough, but also in adults after polio, hepatitis B, influenza and pneumococcus vaccines. Although rare in absolute terms, the most frequent complications are autoimmune thrombocytopenia accompanied by haemorrhagic manifestations. Even rarer complications include acquired haemophilia A, thrombotic thrombocytopenic purpura and cytopenia. These complications are thought to be attributable to the dysregulation of the innate and/or adaptive immune system, as a result of signals of damage associated with inflammation induced by the vaccines and antigenic molecular mimesis mechanisms following the activation of autoreactive B and T cells that were dormant prior to vaccination.
Notwithstanding the rarity of these complications, they are well-known to paediatricians in particular, but a completely different phenomenon is the recent and entirely new syndrome resulting from a neoformation of autoantibodies directed towards a cationic protein like platelet factor 4, which is accompanied more often by catastrophic occurrences of thrombosis than by occurrences of haemorrhages linked to thrombocytopenia. This syndrome, which is known as VITT (vaccine-induced immune thrombotic thrombocytopenia) is caused almost exclusively by COVID-19 vaccines developed with DNA-recombinant techniques which use human or animal viruses as vectors of the information required to produce antibodies against the coronavirus SARS-Cov-2 spike protein. Fortunately, VITT is a very rare syndrome that has been reduced considerably and will hopefully be eliminated by the decision by the regulatory authorities in many countries to avoid using adenoviral vector vaccines in young people who are more at risk of developing this rare complication. VITT gives rise to serious thrombotic phenomena (which mainly affect the visceral veins of the brain and abdomen), as well as brain haemorrhages from thrombocytopenia. Apart from the above-mentioned effective primary preventive measure, a great deal of clinical experience has also been acquired regarding the treatment of VITT, but this remains a very serious complication.

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F. Peyvandi

THROMBOTIC MICROANGIOPATHIES

Thrombotic microangiopathies (TMAs) are a wide spectrum of diseases characterized by thrombocytopenia, microangiopathic hemolytic anemia and widespread ischemic damage due to microvascular thrombosis. TMAs could be life-threatening unless promptly recognized and treated, hence demand a rapid differential diagnosis and initiation of proper therapy, especially in the light of the new targeted therapies available nowadays. Thrombotic thrombocytopenic purpura (TTP) is a rare and severe primary TMA, caused by the congenital or acquired deficiency of ADAMTS13, the von Willebrand factor-cleaving protease. The severity of TTP, the significant recent developments in treatment and the heterogeneity of management worldwide, among other reasons, prompted the International Society of Thrombosis and Hemostasis (ISTH) to promote the draw up of evidence-based guidelines for the diagnosis and treatment of TTP. The new ISTH TTP guidelines were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which provides a framework for rating quality of evidence and grading strength of recommendations in a structured, transparent and comprehensive way. Very recently, the Italian TTP guidelines have been adapted from the ISTH TTP guidelines by the Italian Society of Hematology (SIE). This lecture will provide a brief overview of TMAs and their differential diagnosis and summarize the epidemiology, pathogenesis, diagnosis and management of TTP, focusing on the new ISTH and SIE guidelines.

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M. Napolitano

COVID-19 AND HEMOPHILIA

COVID19 has dramatically modified several aspects of medical care, this is particularly true for patients affected by a chronic, rare disease like haemophilia A and B. Several issues and concerns have been raised during the course of the current pandemic, which include: the relations between physicians and patients; the management of replacement therapies and prophylaxis, with the prompt development of ad hoc recommendations by National and International Societies involved in haemophilia care; advice about vaccines against Sars-CoV2 and their administration; the development of telemedicine and its widespread use. The current presentation describes each of these specific aspects, currently still involving the "new and next future" management of haemophilia.

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G. Sottilotta

NEW THERAPEUTIC HORIZONS IN HEMOPHILIA B: HOW TO GET MORE PROTECTION FOR PATIENTS

What is the rationale for a new concentrate of a Factor IX (FIX) Extended Half Life? The reduction of the Annual Bleeding Ratio (ABR) and the prevention of further hemarthrosis in the target joints through weekly infusions. Other objectives are: the improvement of the joint status and the quality of life thanks to the possibility of reducing the frequency of prophylactic infusions, and the reduction of the risk of inhibitors. Nonacog beta pegol N9-GP (Refixia, Novonordisk) is an increased half-life recombinant FIX (rFIX) that meets all these needs. Refixia is produced in Chinese hamster ovary (CHO) cells by a serum-free manufacturing process. What are its characteristics? Refixia is a purified rFIX) with a 40 kilo Dalton (kDa) polyethylene-glycol (PEG) selectively attached to specific N-linked glycans in the rFIX activation peptide. Once activated, the activation peptide comprising the 40 kDa polyethylene glycol fraction separates, leaving the native factor IX molecule (identical to human FIX) activated. In Europe, Refixia is approved for the treatment and prophylaxis of bleeding in patients aged 12 years and above with haemophilia B. The market placing was preceded by several years of clinical studies. The completed clinical trial program (Paradigm) included one phase 1 trial and four phase 3 multicenter, noncontrolled trials.

All clinical studies have given excellent results in terms of efficacy and safety compared to the other factor IX concentrates already on the market with which they were compared. In a dedicated surgery trial, the haemostatic effect of Refixia during surgery was confirmed with a 100% success rate in the 15 major surgeries in the trials. All minor surgeries evaluated were performed successfully.

Two real-life Canadian studies also found that overall, all patients studied reported favorable experiences after switching to Refixia prophylaxis and a reduced need for the number of infusions for those treated on-demand. The authors conclude that the extended half-life of N9-GP is likely to contribute to improvements in the quality of life.

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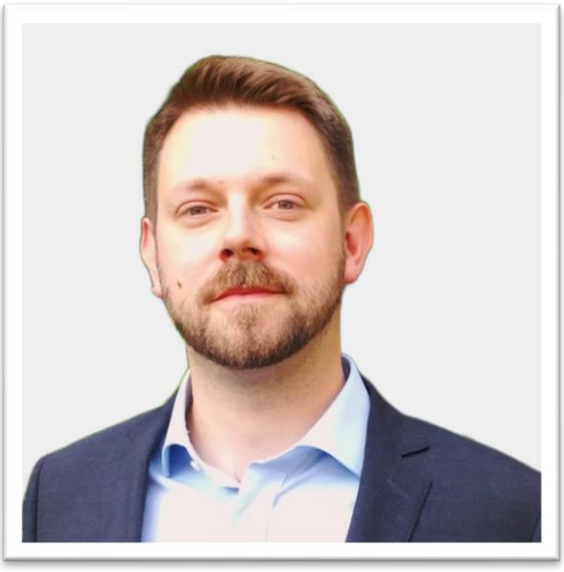
P. A. Cortesi

COST OF HAEMOPHILIA TREATMENT IN THE ERA OF NEW EXTENDED HALF-LIFE PRODUCTS AND NON-FACTOR REPLACEMENT THERAPY.

The cost associated with a clinical condition can be categorized into three main categories: direct, indirect, and intangible. Direct costs are items that are more closely related to the disease and its treatment (e.g. drug treatment, hospitalizations, surgery, physiotherapy), indirect costs that are related to productivity variation due to the disease and its management, and intangible costs that refer to the consequences of a disease and of a medical treatment on individuals' quality of Life. Haemophilia is a condition with significant burdens and costs associated with all these three categories; however, the focus has always been on the direct costs associated with the drug treatment.



The average cost of prophylaxis treatment of haemophilia patients has ranged from €180,000 to more than €800,000 based on the presence and absence of inhibitors and on patient's characteristics. Recently the availability of new treatments has had a significant impact on clinical outcomes and patients' quality of life but also on the associated costs. The first non-factor replacement therapy approved for haemophilia A with inhibitor has been associated with a significant cost reduction of these patients due to the lower cost of this treatment compared to the bypassing agents. Furthermore, the availability of different ended half-life products has also reported a potential reduction of FXII and FIX IU consumption with overall lower costs also due to the lower price per IU associated with these new products. The availability of more efficient and effective treatment has created a situation of a potential improvement of haemophilia management and patients' quality of life with no impact on overall budget or even a budget reduction. Specific real life data are needed to assess if this potential impact will be realized. A better understanding of the value created could be reached assessing changes in costs and the associated clinical variations and outcomes reported by patients.

COMITATO ORGANIZZATORE LOCALE

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