Blood 144 (2024) 1138–1140

The 66th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

114.SICKLE CELL DISEASE, SICKLE CELL TRAIT, AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Data Driven Research through the European RADeep Registry and the Use of Artificial Intelligence Towards Personalized Medicine in Sickle Cell Disease

Anna Collado Gimbert, MD[1,2], Sara Reidel, MSc[1], Patricia Alonso de Apellániz, MSc[3], Federico Alvarez, Prof, PhD[4], Borja Arroyo Galende, MSc[5], David Beneitez, MD[6,7], Bart J. Biemond, MD PhD[8], Maria Paola Boaro, MD[9], Betzabel Cajiao Garcia, MSc[10], Gastone Castellani, PhD[11], Elena Cela, MD PhD[12], Marjon H. Cnossen, MD PhD[13], Piero Fariselli, PhD[14], Karin Fijnvandraat, MD PhD[15], Béatrice Gulbis, MD PhD[16,17], Amira Idrizovic, MSc, PhD[1,18], Petros Kountouris, PhD[19], Vincent Malcor Deydier De Pierrefeu, PhD[20], Sandra Manceau, PhD[21], Elisabetta Mezzalira, RN, MS, PhD[22], Erfan Nur, MD PhD[23], Kalia Orphanou, PhD[24], Juan Parras, PhD[25], Salvador Payán-Pernía, MD[26], Anne-Laure Pham Hung D'Alexandry D'Orengiani, PhD[27], Minke A.E. Rab, MDPhD[28], Giulia Reggiani, MD[29], Anita W. Rijneveld, MD PhD[30], Cesare Rollo, PhD[14], Anna Ruiz Llobet, MD[31], Tiziana Sanavia, PhD[14], Saskia EM Schols, MD PhD[32], Stella Tamana, PhD[24], Marissa J.M. Traets, MD[33], Silvia Uribe, PhD[34], Sigrid van der Veen, MSc[35], Santiago Zazo, Prof.,PhD[36], Pablo Bartolucci, MDPhD[37], Mariane De Montalembert, MDPhD[38], Raffaella Colombatti, MD PhD[39], Eduard J. Van Beers, MD PhD[40,41], Maria del Mar Mañú-Pereira, PhD[1]

[1] Rare Anemia Disorders Research Laboratory, Cancer and Blood Disorders in Children, Vall d'Hebron Research Institute / Vall d'Hebron University Hospital, Barcelona, Spain
[2] Pediatric Oncology and Hematology, Vall d'Hebron Barcelona Hospital, Barcelona, Spain
[3] Information Processing and Telecommunications Center, Universidad Politécnica de Madrid, Madrid, Spain
[4] Universidad Politécnica de Madrid, Madrid, Spain
[5] Grupo de Aplicación de las Telecomunicaciones Visuales, Universidad Politécnica de Madrid, Madrid, Spain
[6] Hematology Department, Vall d'Hebron Hospital Universitari/Vall d'Hebron Research Institute (VHIR)/Vall d'Hebron Institute of Oncology (VHIO)/Universitat Autònoma de Barcelona (UAB)/ERN-EuroBloodNet, Barcelona, Spain
[7] Vall d'Hebron Institute of Oncology, Vall d'Hebron Hospital Universitari, Universitat Autonoma de Barcelona, Barcelona, Spain
[8] Department of Hematology, Amsterdam University Medical Centers, Amsterdam, Netherlands
[9] Department of Women's and Children's Health, Padova University, Padova, Italy
[10] Center for Benign Hematology, Thrombosis and Hemostasis - Van Creveldkliniek, University Medical Center Utrecht, Utrecht University, University Medical Center Utrecht, Utrecht, Netherlands
[11] Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
[12] Pediatric Hematology and Oncology, Hospital Gregorio Marañón. Universidad Complutense de Madrid, Madrid, Spain
[13] Department of Pediatric Hematology and Oncology, Erasmus MC Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, Netherlands
[14] Computational Biomedicine Unit, Department of Medical Sciences, University of Torino, Turin, Italy
[15] Department of Pediatric Hematology, Amsterdam UMC, Emma Children's Hospital, Amsterdam, Netherlands
[16] Hopital Erasme U.L.B, Brussels, BEL
[17] Centre of Human genetics, Hôpital Universitaire de Bruxelles, Université Libre de Bruxelles, Brussels, Belgium
[18] Genetics and Microbiology department, Universitat Autonoma de Barcelona, Barcelona, Spain
[19] Molecular Genetics Thalassaemia Department, The Cyprus Institute of Neurology and Genetics, Nicosia, CYP
[20] Sickle Cell Referral Center, Department of Internal Medicine, Henri-Mondor University Hospital- UPEC, AP-HP, Creteil, France
[21] Laboratoire d'Excellence GR-Ex, Paris, France., Paris, France
[22] Pediatric Hematology, Oncology and Stem Cell Transplant Division, Maternal and Child Health Department, Università degli Studi di Padova, Padova, Italy
[23] Department of Hematology, Amsterdam UMC location University of Amsterdam, Amsterdam, Netherlands
[24] Molecular Genetics Thalassaemia Department, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus

[25] Information Processing and Telecommunications Center, ETSI Telecomunicación, Universidad Politécnica de Madrid, Madrid, Spain
[26] Servicio de Hematologia, Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBiS), Sevilla, Spain
[27] University Paris-Est-Créteil, IMRB, Inserm U955, Laboratory of excellence LABEX, Henri Mondor University Hospitals, APHP, Sickle Cell Referral Center-UMGGR, Créteil, FRA
[28] Department of Hematology, University Medical Center Utrecht, Utrecht, Netherlands
[29] Department of Women's and Children's Health, University of Padua, Padova, Italy
[30] Department of Hematology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, Netherlands
[31] Pediatric Hematology, Hospital Sant Joan de Déu, Barcelona, Barcelona, ESP
[32] Department of Hematology, Radboud University Medical Center, Nijmegen, Netherlands
[33] Central Diagnostic Laboratory - Research, University Medical Center Utrecht, Utrecht, Netherlands
[34] Escuela Técnica Superior de Ingeniería de Sistemas Informáticos-Departamento de Sistemas Informáticos, Universidad Politécnica de Madrid, Madrid, Spain
[35] Center for Benign Hematology, Thrombosis and Hemostasis - Van Creveldkliniek, University Medical Center Utrecht, Utrecht, Netherlands
[36] Centro de I+D+i en Procesado de la Información y Telecomunicaciones (IPTC), Universidad Politécnica de Madrid, Madrid, Spain
[37] University Paris-Est-Créteil, IMRB, Inserm U955, Henri Mondor University Hospitals, APHP, Sickle Cell Referral Center-UMGGR, Creteil, France
[38] Department of General Pediatrics and Pediatric Infectious Diseases, Sickle Cell Center, Necker-Enfants Malades Hospital, Neuilly, France
[39] Department for Woman's and Child's Health, University of Padova, Padova, Italy
[40] Department of Hematology, Van Creveldkliniek, University Medical Center Utrecht, Utrecht, Netherlands
[41] Center for Benign Hematology, Thrombosis and Hemostasis - Van Creveldkliniek, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands

Background:
Sickle cell disease (SCD) is a life-threatening genetic inherited disease considered rare in the European Union (EU). Its complex mechanisms lead to highly variable clinical expression, encompassing in a majority of patients severe acute events and progressive organ damage with premature death. The lack of large datasets combining standardized clinical and research data in real settings hampers the identification of reliable biomarkers and endpoints to monitor disease progression, assess safety and efficacy of new therapies and regulatory decision making.
The RADeep, Rare Anemia Disorders European Epidemiological Platform, aims to collect large amount of highly standardized clinical data to enable data driven outcome research through the linkage of real-world data (RWD) repositories across EU.
Artificial Intelligence (AI) based models for SCD progression, severity classification, response to treatments and generation of synthetic data are being developed through Genomics and Personalized Medicine for all (GenoMed4All) and Synthetic Generation of Haematological Data Over Federated Computing Frameworks (SYNTHEMA) EU-funded projects.

Methodology:
The first large EU SCD dataset includes clinical (n=100), laboratory (n=65) and research data i.e. GWAS, tNGS, metabolomics and rheology from 5 repositories (France (2), Italy, Spain and The Netherlands); all data has been generated through standardized methodologies. To ensure relevance, coherence, timeliness, completeness, coverage and reliability of the minimal dataset for the development of the AI models, a data management and quality analysis plan were applied at data source and centrally. Descriptive analysis of a) hemolysis related parameters b) hydroxyurea uptake and c) number of vaso-occlusive events (VOE) have been performed dis-aggregated by age ranges 0-11yo and ≥12yo, beta and alpha globin genotypes and sex.

Results:
Standardized data on 1,150 SCD patients has been gathered through RADeep. The cohort is representative of all age groups: 0-11yo=29.5%, 12-17yo=17.8%, 18-54yo=45.6% and ≥55yo =7.1%. Sex at birth distribution is balanced (F=53.4%) except for ≥55yo (F=73.2%). SCD subdiagnosis resulted on 864 SS (75%), 151 SC (13%), 113 Sbeta (9.8%), 17 SOtherHb (1.5%) and 5 S-HPFH (0.4%). Beta and alpha globin genotypes are collected in 97% and 87% of the patients respectively (missing data is being generated). Discrepancies between SCD subdiagnosis and beta globin genotype reported data, initially found in 6.1% of the records, were solved after data source verification. Proportions of one alpha and two alpha deletions were 21 and 3.5%, respectively.
Dis-aggregated descriptive analysis showed higher hydroxyurea uptake rates and Hb concentration levels across all genotypes and age groups than previously reported. Age group 0-11yo: SS=HU89.4%, Hb9.0g/dL; SC=HU20%,Hb11g/dL; Sbeta0=HU84.6%,Hb10g/dL and Sbeta+=HU11.1%,Hb10.4g/dL. Age group ≥12yo: SS=HU80.5%,Hb9.0g/dL; SC=HU22.6%, Hb11.5g/dL; Sbeta0=HU78.9%,Hb9.9g/dL and Sbeta+=HU35.7%,Hb11.3g/dL.
The proportion of patients aged 0-11yo with at least 1 VOE in the last 2 years was SS =25%, SC=20%, Sbeta0=15.4% and Sbeta+=0%. For patients ≥12yo SS =46%, SC=33%, Sbeta0=28.9% and Sbeta+=21.4%. Interestingly SC genotype in <12yo showed similar frequencies as SS while in ≥12yo was markedly lower.

SS male patients ≥12yo presented with higher values of total Hb if α-/α- or $\alpha\alpha$/α- was associated whereas this difference was not evident in the female group.

Conclusions

Standardization and quality assurance of RWD from multiple cross border data sources is a crucial step to advance data driven clinical research and improved care pathways in SCD; RADeep EpiData reported 26,892 patients with SCD in regular follow-up from 324 clinical sites in 12 EU countries.

The RADeep SCD dataset will enable to validate hypothesis on clinical outcome research and open the door for personalized medicine in SCD through the development of AI models for recurrent VOEs, acute chest syndrome and cerebral silent infarct. Resulting models can be validated in clinical settings at data providers contributing to the RADeep, currently 87 medical centres in 8 EU countries, that have collected standardized clinical data for 3,000 SCD patients in 2024. RADeep is currently working to get datasets qualified by EMA for regulatory purposes and to integrate patient self-reported outcomes in SCD.

Disclosures Collado Gimbert: *Agios:* Research Funding; *Novartis:* Research Funding; *Bristol myers squibb:* Research Funding; *Novonordisk:* Consultancy; *Pfizer:* Consultancy. **Reidel:** *Agios:* Research Funding; *Bristol Myers Squibb:* Research Funding; *Novartis:* Research Funding. **Beneitez:** *Vertex Pharmaceuticals:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Novo Nordisk:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Bristol Myers Squibb (Celgene):* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Sobi:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Novartis:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Agios:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Biemond:** *pfizer:* Consultancy, Research Funding; *sanofi:* Honoraria; *novartis:* Research Funding; *BMS:* Consultancy, Research Funding; *novo nordisk:* Honoraria. **Cela:** *Pfizer:* Consultancy; *Vertex:* Consultancy, Speakers Bureau. **Cnossen:** *Takeda:* Research Funding, Speakers Bureau; *Pfizer:* Research Funding, Speakers Bureau; *Bayer:* Research Funding, Speakers Bureau; *Novartis:* Research Funding, Speakers Bureau; *CSL Behring:* Research Funding, Speakers Bureau; *Novo Nordisk:* Research Funding, Speakers Bureau; *Nordic Pharma:* Research Funding, Speakers Bureau; *Roche:* Membership on an entity's Board of Directors or advisory committees; *Bayer:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees. **Fijnvandraat:** *SOBI:* Consultancy, Research Funding; *Sanofi:* Consultancy; *NovoNordisk:* Consultancy, Research Funding; *Roche:* Consultancy; *CSL Behring:* Research Funding; *ISTH SSC:* Membership on an entity's Board of Directors or advisory committees. **Gulbis:** *Novartis:* Research Funding; *Agios Pharmaceutical:* Research Funding; *Bristol-Myers Squibb SA:* Research Funding. **Idrizovic:** *Agios:* Research Funding; *Novartis:* Research Funding; *Bristol Myers Squibb:* Research Funding. **Kountouris:** *Agios:* Research Funding. **Nur:** *vertex:* Speakers Bureau; *Novartis:* Research Funding. **Payán-Pernía:** *Sanofi:* Honoraria; *Abbvie:* Other: travel grant; *Vifor Pharma:* Other: travel grant; *Vertex Pharmaceuticals:* Consultancy; *Pfizer:* Consultancy. **Rab:** *Pfizer:* Research Funding; *RR Mechatronics:* Research Funding; *Agios:* Research Funding. **Rijneveld:** *Vertex:* Other: Advisory board. **Traets:** *Agios Pharmaceuticals:* Research Funding. **Bartolucci:** *Innovhem:* Other: Founder; *Pfizer:* Consultancy; *Bluebird:* Consultancy; *Roche:* Consultancy; *Novartis:* Consultancy, Other: member advisory board and member steering commitee; *Emmaus:* Consultancy; *JazzPharma:* Consultancy; *Addmedica:* Consultancy, Other: member advisory board. **De Montalembert:** *vertex:* Membership on an entity's Board of Directors or advisory committees; *Theravia:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *novartis:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Colombatti:** *Pfizer:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Forma Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Novo Nordisk:* Membership on an entity's Board of Directors or advisory committees; *Vertex/Addmedica:* Membership on an entity's Board of Directors or advisory committees; *Agios:* Membership on an entity's Board of Directors or advisory committees. **Van Beers:** *Agios Pharmaceuticals, Inc.:* Consultancy, Research Funding. **Mañú-Pereira:** *Bristol Myers Squibb:* Research Funding; *Agios:* Other: Advisory board, Research Funding; *Novartis:* Research Funding.

https://doi.org/10.1182/blood-2024-203331