Transfusion Medicine and Hemotherapy

Editorial

Transfus Med Hemother 2024;51:289–291
DOI: 10.1159/000540110

Received: June 25, 2024
Accepted: June 27, 2024
Published online: August 21, 2024

Classical Haematology: Dynamic Development at the Interface of Transfusion Medicine and Haematology

Hubert Schrezenmeier[a, b]

[a]Institute of Transfusion Medicine, University of Ulm, Ulm, Germany; [b]Institute of Transfusion Medicine and Immunogenetics Ulm, German Red Cross Blood Transfusion Service Baden-Württemberg-Hessen and University Hospital Ulm, Ulm, Germany

Keywords
Haemolytic anaemia · Bone marrow failures · Complement inhibitors · Gene therapy · Telomerase

This special issue of *Transfusion Medicine and Haemotherapy* presents a range of disorders that are of particular clinical relevance to haematologists and transfusion medicine specialists alike paroxysmal nocturnal haemoglobinuria, thrombotic microangiopathies, immune haemolytic anaemias, sickle cell disease, and bone marrow failure syndromes with genetic predisposition. All articles were written by renowned experts in their respective fields and represent an up-to-date review of the pathophysiology, diagnosis, and treatment of these disorders. All the articles have in common that they show groundbreaking new developments in the treatment of these disorders. For many patients with these rare, non-malignant, chronic disorders presented in this special issue, the only curative treatment approach was allogeneic stem cell transplantation. However, due to the morbidity and mortality of this procedure and due to the lack of a suitable donor, the majority of patients with the relevant diagnoses were not eligible for this therapy. In many cases, this only left limited therapeutic options – either only supportive care or specific treatments with only a moderate effect overall.

In the past, these disorders, which are presented in this issue, often have been classified as benign or non-malignant haematological disorders. However, one can only agree with the authors of a recent "viewpoint" in *Lancet Haematology* [1]. They stated: "*use of the terms benign and non-malignant to describe this field dismisses patient suffering, dampens trainee interest, and diminishes the field as a whole. We propose more uniform adoption of the term classical haematology by organisations, academic divisions, and clinical practices, as this term avoids the conscious and unconscious devaluation of the "benign" and "non-malignant" descriptors*" [1]. This issue shall support this notion by demonstrating the scientific advantage and its great importance for the well-being of patients in the field of classical haematology.

Over the last two decades, we have seen how molecularly targeted therapies and newly developed immunotherapies have been increasingly introduced in the treatment of malignant haematological diseases and oncological diseases. These have improved the prognosis of patients with malignant diseases, in some cases with very significant changes compared to the previous era.

This dynamic of development of disease-modifying, molecularly targeted therapies also applied to classic haematology – albeit often with less notice. Let us look at a few examples, which are presented in details in this issue.

For the ultrarare disease paroxysmal nocturnal haemoglobinuria, the first targeted disease-modifying therapy with the first-in-class C5 inhibitor eculizumab was introduced in 2007 [2]. A further C5 monoclonal antibody, ravulizumab, was approved in 2019 [3, 4]. And now in the current year, within a few weeks we have seen in Europa an extension of the indication of the C3 inhibitor pegcetacoplan [5] and approvals of the factor B inhibitor iptacopan [6] and the factor D inhibitor danicopan [7]. The article by Hillmen et al. [2] summarizes this development and also

karger@karger.com
www.karger.com/tmh

Correspondence to:
Hubert Schrezenmeier, h.schrezenmeier@blutspende.de

looks at other complement inhibitors that are currently in clinical development. This was only possible because molecular targets for optimizing complement inhibition were identified through careful clinical observation in combination with basic research on the complement system.

In the article on microangiopathic anaemias by M. Bommer [8], the latest findings on the pathophysiology of thrombotic microangiopathies are presented. These clinical pictures are also a good example of how findings from the laboratory have led to the development of new therapies, be it C5-directed complement inhibition in atypical haemolytic uraemic syndrome [9] or caplacizumab [10], an antibody against von Willebrand factor, for treatment of thrombotic thrombocytopenic purpura.

This dynamic of the availability of new treatment options also applies to autoimmune haemolytic anaemia. W. Barcellini and B. Fattizzo [11] provide an overview of B-cell-depleting and plasma cell-targeted therapies and in particular the development of Fc receptor blockers (nipocalimab) and targeted complement inhibitors (sutimlimab, ruliprubart, pegcetacoplan, or iptacopan) [12, 13].

The article by J.B. Kunz and L. Tagliaferri [14] provides a comprehensive overview of sickle cell disease, particularly with regard to therapy. The findings on the pathomechanism of this disease have also led to the development of new therapeutic options, be it voxelotor [15], a haemoglobin modulator, be it crizanlizumab [16], a monoclonal antibody against P-selectin, and, above all, the current development of a cell therapy based on gene editing (Exa-cel) with targeted CRISPR/Cas-9-based silencing of BCL11A in order to achieve re-expression of HbF [17, 18]. The studies recently published in the *New England Journal of Medicine* on Exa-cel in sickle cell disease [17] and thalassaemia [18] represent the beginning of a new era [19] – the first use of CRISPR/Cas-9 gene therapy, which has now been approved in some countries.

The article by Rolles et al. [20] highlights that 10% of bone marrow failure syndromes in adults have a congenital cause and a very broad spectrum of genes can be affected, with a focus on components of the telomerase complex. Very different mutations can be present [21]. The article provides a very clear overview of currently known mutations and the corresponding clinical phenotype. This will help to recognize this still frequently undiagnosed condition as it is also of great importance for prognosis and treatment decisions. The article also emphasizes the importance and strength of genetic diagnostics.

The topics presented in this issue together and individually represent important developments in classical haematology and transfusion medicine according to the following: (i) Basic research focusing on the understanding of the molecular pathophysiology of these diseases paved the way for the identification of molecular targets. (ii) These findings were the basis for the successful development of molecularly targeted therapies, which allow either a curative option or at least a very significant disease modification that goes far beyond the more supportive therapy options available for these diseases until recently. (iii) Immunohaematological and genetic diagnostics are essential for the early diagnosis of these diseases with their multiple subentities. This is key to allow patients early access to the new drugs that can change patients' lives.

Despite these developments, there is still a medical need to further improve therapies – also in haemolytic disorders and bone marrow failure syndromes. This special issue summarizing successful development in many disorders at the edge of haematology and transfusion medicine shall motivate to continue this success story.

Conflict of Interest Statement

H.S. is the inventor of a patent application that describes the use of complement inhibitors for therapeutic applications; received honoraria for speaking at symposia organized by Alexion Pharmaceuticals and Novartis (all payments to the institution); served on advisory committees for Alexion AstraZeneca Rare Diseases, Sanofi, Sobi, Novartis, Amgen, and Omeros; and received research funding from Alexion Pharmaceuticals (all payments to the institution).

Funding Sources

There are no funding sources.

Author Contributions

This article was written by H.S.

References

1 Al-Samkari H, Loren AW, Lee AI. The case for classical haematology: the impact of a name and the future of a field. Lancet Haematol. 2022;9(6):e455–9. https://doi.org/10.1016/S2352-3026(22)00096-5

2 Hillmen P, Young NS, Schubert J, Brodsky RA, Socie G, Muus P, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2006;355(12):1233–43. https://doi.org/10.1056/NEJMoa061648

3 Kulasekararaj AG, Hill A, Rottinghaus ST, Langemeijer S, Wells R, Gonzalez-Fernandez FA, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood. 2019;133(6):540–9. https://doi.org/10.1182/blood-2018-09-876805

4 Lee JW, Sicre de FF, Wong Lee LL, Pessoa V, Gualandro S, Fureder W, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood. 2019;133(6):530–9. https://doi.org/10.1182/blood-2018-09-876136

5 Hillmen P, Szer J, Weitz I, Roth A, Hochsmann B, Panse J, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2021;384(11):1028–37. https://doi.org/10.1056/NEJMoa2029073
6 Peffault de LR, Roth A, Kulasekararaj AG, Han B, Scheinberg P, Maciejewski JP, et al. Oral iptacopan monotherapy in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2024;390(11):994–1008. https://doi.org/10.1056/NEJMoa2308695
7 Lee JW, Griffin M, Kim JS, Lee Lee LW, Piatek C, Nishimura JI, et al. Addition of danicopan to ravulizumab or eculizumab in patients with paroxysmal nocturnal haemoglobinuria and clinically significant extravascular haemolysis (ALPHA): a double-blind, randomised, phase 3 trial. Lancet Haematol. 2023;10(12):e955–65. https://doi.org/10.1016/S2352-3026(23)00315-0
8 Bommer M. The differential diagnosis of thrombotic microangiopathy. Transfus Med Hemother. 2024. Submitted.
9 Legendre CM, Licht C, Muus P, Greenbaum LA, Babu S, Bedrosian C, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med. 2013;368(23):2169–81. https://doi.org/10.1056/NEJMoa1208981
10 Peyvandi F, Scully M, Kremer Hovinga JA, Cataland S, Knobl P, Wu H, et al. Caplacizumab for acquired thrombotic thrombocytopenic purpura. N Engl J Med. 2016;374(6):511–22. https://doi.org/10.1056/NEJMoa1505533
11 Barcellini W, Fattizzo B. Autoimmune hemolytic anemias: challenges in diagnosis and therapy. Transfus Med Hemother. 2024. https://doi.org/10.1159/000540475
12 Roth A, Barcellini W, D'Sa S, Miyakawa Y, Broome CM, Michel M, et al. Sutimlimab in cold agglutinin disease. N Engl J Med. 2021;384(14):1323–34. https://doi.org/10.1056/NEJMoa2027760
13 Roth A, Barcellini W, D'Sa S, Miyakawa Y, Broome CM, Michel M, et al. Complement C1s inhibition with sutimlimab results in durable response in cold agglutinin disease: CARDINAL study 1-year interim follow-up results. Haematologica. 2022;107(7):1698–702. https://doi.org/10.3324/haematol.2021.279812
14 Kunz JB, Tagliaferri L. Sickle cell disease. Transfus Med Hemother. 2024. https://doi.org/10.1159/000540149
15 Vichinsky E, Hoppe CC, Ataga KI, Ware RE, Nduba V, El-Beshlawy A, et al. A phase 3 randomized trial of voxelotor in sickle cell disease. N Engl J Med. 2019;381(6):509–19. https://doi.org/10.1056/NEJMoa1903212
16 Ataga KI, Kutlar A, Kanter J. Crizanlizumab in sickle cell disease. N Engl J Med. 2017;376(18):1796. https://doi.org/10.1056/NEJMc1703162
17 Frangoul H, Locatelli F, Sharma A, Bhatia M, Mapara M, Molinari L, et al. Exagamglogene autotemcel for severe sickle cell disease. N Engl J Med. 2024;390(18):1649–62. https://doi.org/10.1056/NEJMoa2309676
18 Locatelli F, Lang P, Wall D, Meisel R, Corbacioglu S, Li AM, et al. Exagamglogene autotemcel for transfusion-dependent β-thalassemia. N Engl J Med. 2024;390(18):1663–76. https://doi.org/10.1056/NEJMoa2309673
19 Daley GQ. Welcoming the era of gene editing in medicine. N Engl J Med. 2024;390(18):1642–5. https://doi.org/10.1056/NEJMp2314279
20 Rolles B, Tometten M, Meyer R, Kirschner M, Beier F, Brümmendorf TH. Inherited telomere biology disorders: pathophysiology, clinical presentation, diagnostics, and treatment. Transfus Med Hemother. 2024:1–18. https://doi.org/10.1159/000540109
21 Tometten M, Kirschner M, Meyer R, Begemann M, Halfmeyer I, Vieri M, et al. Identification of adult patients with classical dyskeratosis congenita or cryptic telomere biology disorder by telomere length screening using age-modified criteria. Hemasphere. 2023;7(5):e874. https://doi.org/10.1097/HS9.0000000000000874