

DRUG PROFILE**PLASMA-DERIVED THERAPEUTIC PROTEINS IN PEDIATRICS - PART II**

* **Jeeson C Unni**
** **Aarthi Ramesh**

Abstract: *Part II of the deliberations on PDTP therapies will deal with issues related to the less commonly used products including thrombin for local hemostasis, Von Willebrand factor for treatment of Von Willebrand disease and antithrombin for acquired antithrombin deficiency associated with major cardiac surgery, also, alpha-1 antitrypsin for alpha-1 antitrypsin deficiency, C1 esterase inhibitor concentrate for hereditary angioedema or C1 esterase deficiency and fibrinogen concentrate for the management of congenital fibrinogen deficiency.*

Keywords: *Thrombin, Von Willebrand factor, Antithrombin, Alpha-1 antitrypsin, C1 esterase inhibitor concentrate, Fibrinogen concentrate.*

Points to remember

- *Plasma-derived therapies, including those for rare diseases, are being used in clinical practice and pediatricians need to be updated.*
- *With advances in Recombinant DNA technology, plasma-derived products remain vital and play a significant role in improving patient outcomes.*
- *Emphasis must be made to ensure that these therapies are available, despite challenges in supply.*
- *Continuous research and development is required to explore new fractionation processes and improve quality control measures.*
- *To enhance effectiveness of PDTPs.*
- *Population suffering from rare coagulation disorders with PDTP / rare orphan diseases, have treatment options however limited in supply.*

References

1. Brister SJ, Ofosu FA, Buchanan MR. Thrombin: its key role in thrombogenesis: implications for its inhibition clinically. Boca Raton, FL: CRC Press; 1994
2. Ham SW, Lew WK, Weaver FA. Thrombin use in surgery: an evidence-based review of its clinical use. J Blood Med. 2010; 1:135-42. doi: 10.2147/JBM.S6622. Epub 2010 Jul 22. Retraction in: J Blood Med. 2022 Mar 21;13:165-166. doi: 10.2147/JBM.S366691. PMID: 22282693; PMCID: PMC3262329.
3. Lawson JH. The clinical use and immunologic impact of thrombin in surgery. Semin Thromb Hemost. 2006 Apr; 32(Suppl 1):98-110. doi: 10.1055/s-2006-939559.
4. Patterson C, Stouffer GA, Madamanchi N, Runge MS. New tricks for old dogs: nonthrombotic effects of thrombin in vessel wall biology. Circ Res. 2001; 88(10): 987-997. doi: 10.1161/hh1001.091447

* Editor-in-Chief,
IAP Drug Formulary,
Senior Lead consultant

** Specialist,
Department of Pediatrics and Neonatology,
Aster Med City,
Kochi.
email: jeeson1955@gmail.com

5. Dahlback B. Blood coagulation. *Lancet*. 2000; 355 (9215):1627-1632. doi: 10.1016/S0140-6736(00)02225-X
6. Flaherty MJ, Henderson R, Wener MH. Iatrogenic immunization with bovine thrombin: a mechanism for prolonged thrombin times after surgery. *Ann Intern Med*. 1989;111(8):631-634. doi: 10.7326/0003-4819-111-8-631.
7. Zehnder JL, Leung LL. Development of antibodies to thrombin and factor V with recurrent bleeding in a patient exposed to topical bovine thrombin. *Blood*. 1990; 76(10): 2011-2016
8. Lawson JH, Pennell BJ, Olson JD, Mann KG. Isolation and characterization of an acquired antithrombin antibody. *Blood*. 1990; 76(11):2249-2257
9. Rapaport SI, Zivelin A, Minow RA, Hunter CS, Donnelly K. Clinical significance of antibodies to bovine and human thrombin and factor V after surgical use of bovine thrombin. *Am J Clin Pathol*. 1992; 97(1):84-91. doi: 10.1093/ajcp/97.1.84.
10. US Food and Drug Administration FDA Approves Human Thrombin for Topical Use in Surgery FDA News. Aug 28, 2007. Available at <https://www.fda.gov/media/71754/download>. Accessed on 17/5/25
11. Doria C, Fischer CP, Wood CG, et al. Phase 3, randomized, double-blind study of plasma-derived human thrombin versus bovine thrombin in achieving hemostasis in patients undergoing surgery. *Curr Med Res Opin*. 2008; 24(3):785-794. doi: 10.1185/030079908X273426
12. FDA-RECOTHROM Product Approval Information. Available at: <http://www.fda.gov/Biologics/BloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm089451.htm>. Available at <https://www.fda.gov/media/75321/download>. Accessed on 17/5/25.
13. US Food and Drug Administration FDA News. Jan 17, 2008. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116838.htm>. Available at: https://www.upi.com/Science_News/2008/01/17/FDA-OKs-novel-surgical-clotting-solution/90481200600937/ Accessed on 17/5/25
14. Chapman WC, Lockstadt H, Singla N, Kafie FE, Lawson JH. Phase 2, randomized, double-blind, placebo-controlled, multicenter clinical evaluation of recombinant human thrombin in multiple surgical indications. *J Thromb Haemost*. 2006; 4(9):2083-2085. doi: 10.1111/j.1538-7836.2006.02067.x.
15. Zhu H, Hoppensteadt D, Adiguzal C, Jeske W, Messmore H, Fareed J. Cross Reactivity of Human Recombinant thrombin (Recothrombin) to Antibovine Thrombin Antibodies. Clinical Implications. *FASEB J*. 2009 Apr 1; 23:569, 511. 1 MeetingAbstracts.
16. Singla NK, Ballard JL, Moneta G, Randleman CD, Jr, Renkens KL, Alexander WA. A phase 3b, open-label, single-group immunogenicity and safety study of topical recombinant thrombin in surgical hemostasis. *J Am Coll Surg*. 2009; 209(1):68-74. doi: 10.1016/j.jamcollsurg.2009.03.016.
17. King Pharmaceuticals Inc Prescribing information: Thrombin-JMI, 2007.
18. Sabel M, Stummer W. The use of local agents: Surgicel and Surgifoam. *Eur Spine J*. 2004; 13(Suppl 1):S97-S101. doi: 10.1007/s00586-004-0735-z.
19. Schwartz M, Madariaga J, Hirose R, et al. Comparison of a new fibrin sealant with standard topical hemostatic agents. *Arch Surg*. 2004; 139(11):1148-1154. doi: 10.1001/archsurg.139.11.1148
20. Glickman M, Gheissari A, Money S, Martin J, Ballard JL. A polymeric sealant inhibits anastomotic suture hole bleeding more rapidly than gelfoam/thrombin: results of a randomized controlled trial. *Arch Surg*. 2002; 137(3):326-331. doi: 10.1001/archsurg.137.3.326. discussion 332
21. Taylor LM, Jr, Mueller-Velten G, Koslow A, Hunter G, Naslund T, Kline R. Prospective randomized multicenter trial of fibrin sealant versus thrombin-soaked gelatin sponge for suture- or needle-hole bleeding from polytetrafluoroethylene femoral artery grafts. *J Vasc Surg*. 2003; 38(4):766-771. doi: 10.1016/s0741-5214(03)00474-9.
22. Casari C, Berrou E, Lebreton M, et al. von Willebrand factor mutation promotes thrombocytopenia by inhibiting integrin α IIb β 3. *J Clin Invest*. 2013; 123(12):5071-5081. doi: 10.1172/JCI69458.
23. Castaman G, Goodeve A, Eikenboom J. Principles of care for diagnosis and treatment of von Willebrand disease. *Haematologica*. 2013; 98(5):667-674. doi: 10.3324/haematol.2012.077263
24. Rodeghiero F, Castaman G, Tosetto A. How I treat von Willebrand disease. *Blood*. 2009; 114(6):1158-1165. doi: 10.1182/blood-2009-01-153296
25. Castaman G, Lethagen S, Federici AB, et al. Response to desmopressin is influenced by the genotype and the phenotype in type 1 von Willebrand disease (VWD): results from the European study MCMDM-1 VWD. *Blood*. 2008; 111:3531-3539. doi: 10.1182/blood-2007-08-109231
26. Mannucci PM, Chediak J, Hanna W, Byrnes J, Marlies L, Ewenstein BM, Alphanate Study Group Treatment of von Willebrand disease with high-purity factor VIII/von Willebrand factor concentrate: a prospective, multicenter study. *Blood*. 2002; 99:450-456. doi: 10.1182/blood.v99.2.450

27. Mannucci PM, Kempton C, Millar C, et al. Pharmacokinetics and safety of a novel recombinant human von Willebrand factor manufactured with a plasma-free method: a prospective clinical trial. *Blood*. 2013;122(5):648-657. doi: 10.1182/blood-2013-01-479527
28. Gill JC, Castaman G, Windyga J, et al. Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. *Blood*. 2015; 126(17):2038-2046. doi: 10.1182/blood-2015-02-629873.
29. Natalie Smith, Beth Boulden Warren, Julie Smith, Linda Jacobson, Jennifer Armstrong, Jihye Kim, Jorge Di Paola, Marilyn Manco-Johnson, Antithrombin deficiency: A pediatric disorder, *Thrombosis Research*, Volume 202, 2021, Pages 45-51, ISSN 0049-3848
30. ATryn for Injections: U.S Package Insert. Framingham, MA: GTC Biotherapeutics, Inc.; 2010. Nov.
31. U.S. Food and Drug Administration. Cumulative List of Orphan Products Designations and Approvals. [Accessed May 22,2013];1999.
32. U.S. Food and Drug Administration. Approval Letter-ATryn. [Accessed May 22, 2013]; 2009 Feb 6; Available at: <http://www.fda.gov/Biologics Blood Vaccines/Blood Blood Products/ApprovedProducts/Licensed Products BLAs/Fractionated Plasma Products/ucm134046.htm>.
33. Bassler D, Millar D, Schmidt B. Antithrombin for respiratory distress syndrome in preterm infants. *Cochrane Database Syst Rev*. 2006 Oct 18; 2006(4): CD005383. doi: 10.1002/14651858.CD005383.pub2. PMID: 17054254; PMCID: PMC8885308.
34. Chapman KR, Burdon JG, Piitulainen E, Sandhaus RA, Seersholm N, Stocks JM, Stoel BC, Huang L, Yao Z, Edelman JM, et al.; RAPID Trial Study Group. Intravenous augmentation treatment and lung density in severe α 1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015; 386:360-368.
35. Hubbard RC, McElvaney NG, Sellers SE, Healy JT, Czerski DB, Crystal RG. Recombinant DNA-produced alpha 1-antitrypsin administered by aerosol augments lower respiratory tract antineutrophil elastase defenses in individuals with alpha 1-antitrypsin deficiency. *J Clin Invest* 1989; 84:1349-1354.
36. Hubbard RC, Brantly ML, Sellers SE, Mitchell ME, Crystal RG. Anti-neutrophil-elastase defenses of the lower respiratory tract in alpha 1-antitrypsin deficiency directly augmented with an aerosol of alpha 1-antitrypsin. *Ann Intern Med* 1989; 111:206-212.
37. Strauss P, Stolk J, McElvaney G, Piitulainen E, Seersholm N, Chapman KR, Hopkinson N, MacNee W, Runold M, Vogelmeier C, et al. Phase II/III, double-blind, randomized, placebo-controlled, international study evaluating the safety and efficacy of inhaled, human, α 1-antitrypsin (AAT) in α 1-antitrypsin deficient patients (AATD: update in alpha one deficiency [abstract]. *Am J Respir Crit Care Med* 2014;D38
38. Lykavieris P, et al. Liver disease associated with ZZ alpha1-antitrypsin deficiency and ursodeoxycholic acid therapy in children. *Journal of Pediatric Gastroenterology and Nutrition*. 2008; 47(5):623-9. doi: 10.1097/MPG.0b013e31817b6dfb
39. Feldman A, Sokol RJ. Alpha-1-Antitrypsin Deficiency: An Important Cause of Pediatric Liver Disease. *Lung Health Prof Mag*. 2013; 4(2):8-11. PMID: 27019872; PMCID: PMC4805363.
40. Ivanov I, Matafonov A, Sun MF, Mohammed BM, Cheng Q, Dickeson SK, Kundu S, Verhamme IM, Gruber A, McCrae K, Gailani D. A mechanism for hereditary angioedema with normal C1 inhibitor: an inhibitory regulatory role for the factor XII heavy chain. *Blood*. 2019 Mar 07; 133(10):1152-1163
41. Zanichelli A, Bova M, Coerezza A, Petraroli A, Triggiani M, Cicardi M. Icatibant treatment for acquired C1-inhibitor deficiency: a real-world observational study. *Allergy*. 2012 Aug;67(8):1074-7. doi: 10.1111/j.1398-9995.2012.02853.x.
42. Barmettler S, Li Y, Banerji A. New and evolving therapies for hereditary angioedema. *Allergy Asthma Proc*. 2019 Jan 01; 40(1):7-13
43. C1 Esterase inhibitor deficiency. Royal children's hospital Melbourne, clinical practice guidelines. Available at https://www.rch.org.au/clinicalguide/guideline_index/c1_esterase_inhibitor_deficiency/. Accessed on 17/5/25.
44. icatibant acetate, 30mg, solution for injection in pre-filled syringe (Firazyr®). Scottish Medicines Consortium, NHS Scotland. Available at https://scottishmedicines.org.uk/media/1808/icatibant_firazyr_resubmission_final_february_2012_amended_060312_for_website.pdf. Accessed on 17/5/25.
45. Palla R, Peyvandi F, Shapiro AD. Rare bleeding disorders: diagnosis and treatment. *Blood*. 2015;125(13): 2052-2061. doi: 10.1182/blood-2014-08-532820.
46. Paraboschi EM, Duga S, Asselta R. Fibrinogen as a pleiotropic protein causing human diseases: The mutational burden of A α , B β and γ chains. *Int J Mol Sci*. 2017;18(12):2711. doi: 10.3390/ijms18122711
47. Tziomalos K, Vakalopoulou S, Perifanis V, Garipidou V. Treatment of congenital fibrinogen deficiency: overview and recent findings. *Vasc Health Risk Manag*. 2009; 5: 843-848. doi: 10.2147/vhrm.s5305
48. Bolton-Maggs PHB, Perry DJ, Chalmers EA, Parapia LA, Wilde JT, Williams MD, Collins PW, Kitchen S, Dolan G, Mumford AD. The rare coagulation disorders-Review with guidelines for management from the United Kingdom Haemophilia Centre Doctors'

- Organisation. *Haemophilia*. 2004; 10:593-628. doi: 10.1111/j.1365-2516.2004.00944.x
49. Szanto T, Lassila R, Lemponen M, Lehtinen E, Neerman-Arbez M, Casini A. Whole Blood Thromboelastometry by ROTEM and Thrombin Generation by Genesia According to the Genotype and Clinical Phenotype in Congenital Fibrinogen Disorders. *Int. J. Mol. Sci.* 2021;22:2286. doi: 10.3390/ijms22052286
50. Vakalopoulou S, Rizopoulou D, Zafiriadou E, Perifanis V, Tziomalos K, Lefkou E, Hill M, Dolan G, Garipidou V. Management of acute bleeding in a patient with congenital afibrinogenaemia. *Haemophilia*. 2006;12: 676-678. doi: 10.1111/j.1365-2516.2006. 01340.x
51. Casini A, Undas A, Palla R, Thachil J, De Moerloose P, Subcommittee on Factor XIII and Fibrinogen Diagnosis and classification of congenital fibrinogen disorders: Communication from the SSC of the ISTH. *J. Thromb. Haemost.* 2018; 16:1887-1890. doi: 10.1111/jth.14216.
52. Nascimento B, Goodnough LT, Levy JH. Cryoprecipitate therapy. *Br. J. Anaesth.* 2014;113:922-934. doi: 10.1093/bja/aeu158.
53. Simurda T, Asselta R, Zolkova J, Brunclikova M, Dobrotova M, Kolkova Z, Loderer D, Skornova I, Hudecek J, Lasabova Z, Stasko J, Kubisz P. Congenital Afibrinogenemia and Hypofibrinogenemia: Laboratory and Genetic Testing in Rare Bleeding Disorders with Life-Threatening Clinical Manifestations and Challenging Management. *Diagnostics (Basel)*. 2021 Nov 19; 11(11):2140. doi: 10.3390/diagnostics11.112140. PMID: 34829490; PMCID: PMC8622093.