Letters to the editor

Blood Coagulation and Fibrinolysis 2025, **36**:386–390

Human plasma-derived plasminogen replacement in type 1 plasminogen deficiency: a pediatric case with multisystemic manifestation

Deniz Koçak Göl[a], Veysel Gök[a], Ebru Yılmaz[a], Ekrem Ünal[a,b], Musa Karakükcü[a], Tülin Tiraje Celkan[c] and Alper Özcan[a]

[a]Department of Pediatrics Hematology and Oncology, Erciyes University Faculty of Medicine, Kayseri, [b]Department of Nursing, Faculty of Health Sciences, Hasan Kalyoncu University & Medical Point Hospital, Gaziantep and [c]Liv Hospital Vadistanbul, Clinic of Pediatric Hematology and Oncology, Istanbul, Turkey

Correspondence to Deniz Koçak Göl, MD, Department of Pediatrics Hematology and Oncology, Erciyes University Faculty of Medicine, Kayseri, Turkey.
Tel: +90 5552677108; e-mail: deniz_3858@hotmail.com

Received 7 September 2025 **Accepted** 16 September 2025

The article by Dönmez-Demir *et al.*, 'Novel plasminogen gene mutations in Turkish patients with type I plasminogen deficiency', recently published in *Blood Coagulation and Fibrinolysis*[1], was read with great interest. The study's authors expanded the mutational spectrum of the *PLG* gene in the Turkish population and emphasized the clinical heterogeneity and the timely recognition of this rare disorder. As highlighted in the discussion, treatment options for type 1 plasminogen deficiency remain limited, and management strategies, including plasminogen replacement therapy, are of particular clinical relevance. In this context, we wish to present our paediatric case demonstrating a multisystemic phenotype and favourable clinical response to human plasma-derived plasminogen replacement.

Plasminogen is a protein involved in intravascular and extravascular fibrinolysis, wound healing, cell migration, tissue formation, angiogenesis, and embryogenesis. Type 1 plasminogen deficiency is a rare disease of the fibrinolytic system caused by mutations in the *PLG* gene. It is inherited in an autosomal recessive manner and involves multisystem involvement. The condition's prevalence is approximately 1.6 per million, with a slight predominance in female individuals over male individuals. Its most prominent feature is the formation of fibrin-rich, woody pseudomembranes on mucosal surfaces, particularly in the conjunctiva. *PLG* activity has been demonstrated to trigger plasmin formation and the fibrinolysis process. In addition, activation of *PLG* by urokinase-type plasminogen activator has been shown to promote wound healing and tissue remodelling [2,3,4]. Although nonspecific treatments and surgical interventions are available, plasminogen replacement therapy has recently been introduced.

The following article expounds on the plasminogen replacement therapy process of a patient afflicted with type 1 plasminogen deficiency, a multisystemic clinical condition associated with accumulated fibrin, and intermittent fresh frozen plasma [fresh frozen plasma (FFP)]-tissue plasminogen activator (t-PA) and surgical intervention treatments.

An 8-year-old male patient presented with ocular discharge at the age of 2 months. A biopsy of the membranous lesions in the bilateral conjunctiva led to a diagnosis of lignous conjunctivitis. Due to hydrocephalus, a ventriculoperitoneal shunt was inserted during the neonatal period. The patient was admitted to the hospital due to recurrent respiratory distress. The patient's findings, including lignous conjunctivitis, a history of hydrocephalus and ventriculoperitoneal shunt, and chronic fibrotic changes seen on chest tomography, were accompanied by a plasminogen level of 14% (normal: 70–130%). The TDP support was administered at 10 cc/kg every 10 days. Using topical plasminogen and TDP has been employed in managing lignous conjunctivitis. Pulmonary lavage with TDP and t-PA was performed during bronchoscopy following the detection of wood-like fibrin plugs in the trachea and bronchi. The fibrin plugs were reduced. During subsequent follow-up, the patient exhibited two recurrences of respiratory distress at 6 months and 1 year, respectively, and the aforementioned procedures were repeated. At the age of 3 years, the patient underwent surgical intervention for the removal of anal polyps and abscesses. At the age of 4 years, the patient underwent further surgical intervention for the removal of a fibrin-induced intestinal obstruction and a pseudocyst at the shunt tip. Intraoperative intra-abdominal TDP lavage was performed.

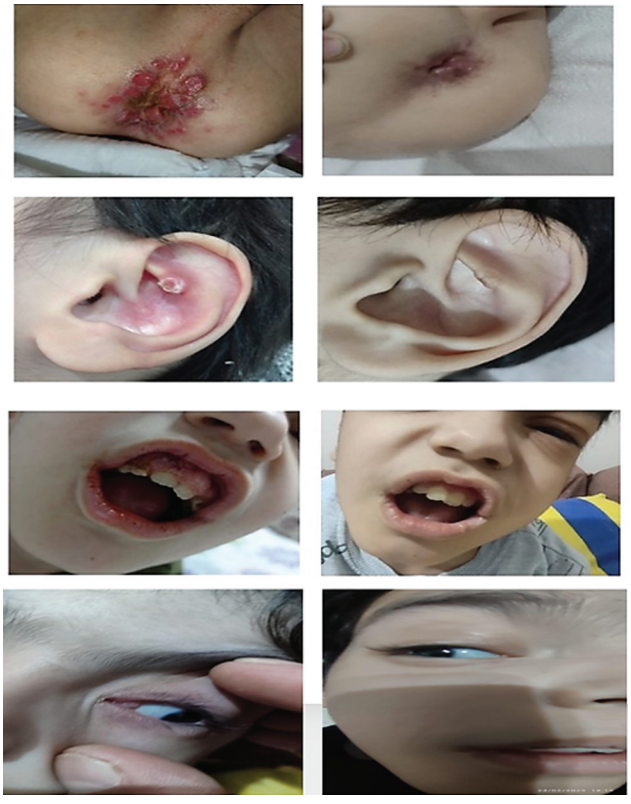
Erosion in the anal region showed a continued upward trend. Genetic analysis revealed a homozygous *PLG* (c.385_391delTCCACTT; p. Ser129LeufsTer99) mutation in the plasminogen gene.

In December 2024, plasminogen replacement therapy was initiated at 6.6 mg/kg/day for 2/7 days. During the 4-month treatment period, a marked improvement in clinical findings was observed after the first eight doses of replacement therapy (Fig. 1). In the fourth month of treatment, an endoscopy was performed in response to recurrent vomiting and dysphagia. A narrowing was detected in the distal oesophagus, and balloon dilation was performed (Fig. 2). The patient continues to receive plasminogen replacement therapy, and there has been an improvement in their gastrointestinal symptoms.

Lignous-pseudomembranous lesions are observed without plasminogen activity within body fluids, and fibrin accumulation within mucous membranes is observed.

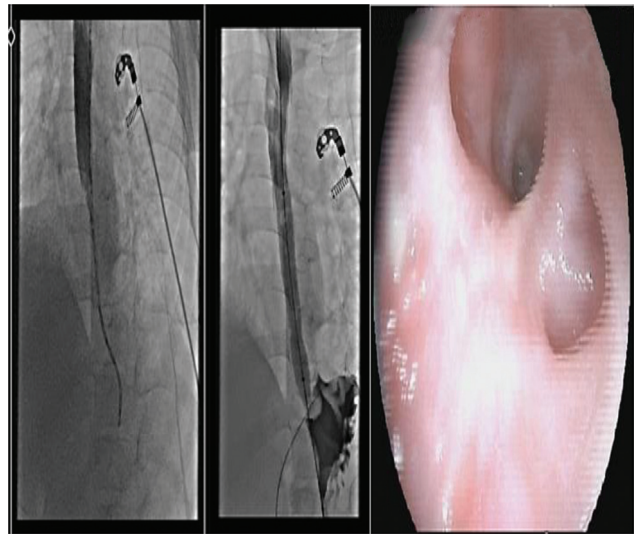
DOI:10.1097/MBC.0000000000001391

Fig. 1



Improvement in clinical findings after eight doses of replacement therapy administered before treatment and at 1 month after treatment.

Fig. 2



The esophageal mucosa was found to be normal proximally; however, it was observed that distally there was marked narrowing and a double lumen appearance. It was not possible to advance through the esophageal lumen.

The most prevalent clinical symptom is lignous conjunctivitis, whilst obstructive hydrocephalus has also been reported in some children [2,5]. The lesions can induce lignous gingivitis in the gums, otitis, and hearing loss due to accumulation in the middle ear and tympanic membrane. Fibrin accumulation in the respiratory tract has been demonstrated to result in respiratory obstruction, respiratory failure, and recurrent pneumonia [6,7]. In this case, the clinical presentation included lignous conjunctivitis, gingivitis, hydrocephalus, and respiratory failure due to pulmonary atelectasis.

In the study conducted by Shapiro *et al.*, the administration of intravenous plasma-derived plasminogen concentrate (6.6 mg/kg intravenously, every 2–4 days for 48 weeks and every 1–7 days for 124 weeks) resulted in the plasma level exceeding 10% of the baseline level. Additionally, all clinical findings were reported to have completely resolved, with the study concluding that the treatment was well tolerated. After the study's findings, the Food and Drug Administration (FDA) recommended the utilization of Ryplazim in 2021 [8].

In 2023, Nasiri *et al.* [4] published a study in which the drug was administered three times a week to an adult patient with plasminogen deficiency, and clinical improvement was observed. In 2024, Decker and colleagues reported on a 33-year-old male patient with a diagnosis of plasminogen deficiency, who exhibited surgical wounds that failed to heal despite standard treatment over a period of 4 months. The patient received six doses of plasminogen replacement therapy, each 6 mg/kg, administered at 3–4 day intervals. A marked improvement was observed in the surgical wounds. This patient is documented as the first in the United States to undergo replacement therapy [3].

In this particular case, representing one of the first in Europe, treatment was initiated at 6.6 mg/kg administered twice weekly. Clinical findings showed signs of improvement after eight replacement doses. In the seventh month of treatment, an increase in quality of life was observed. As in numerous other instances, administering [3,4,9,10] plasminogen concentrate has been efficacious.

In the case study presented, clinical findings demonstrated signs of improvement following the administration of eight replacement doses, and prophylaxis was maintained.

Plasminogen human-TVMH represents the first drug to be approved for treating type 1 plasminogen deficiency. The potential benefits of this approach include enhanced clinical findings and an improvement in the quality of life for patients. The present solution is to be considered more permanent in comparison with both TDP and t-PA. Early access to plasma concentration is also thought to reduce or prevent potential complications.

Acknowledgements

Author contributions: D.K.G. and A.Ö. conceived the idea and analysed the data. D.K.G., V.G., E.Y., and E.Ü.

contributed to the analytical tools. D.K.G. wrote the first draft of the article. A.Ö., V.G., M.K., and T.T.C. critically reviewed the article. All authors approved the final version of the article.

Availability of supporting data: the data supporting this study's findings are available on request from the corresponding author.

The authors alone are responsible for the content and writing of the paper. This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

Conflicts of interest

There are no conflicts of interest.

References

1 Dönmez-Demir B, Celkan T, Sarper N, Deda G, İnce E, Çalişkan Ü, *et al.* Novel plasminogen gene mutations in Turkish patients with type I plasminogen deficiency. *Blood Coagul Fibrinolysis* 2016; **27**:637–644.

2 Shapiro AD, Nakar C, Parker JM, Albert GR, Moran JE, Thibaudeau K, *et al.* Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency. *Blood* 2018; **131**:1301–1310.

3 Decker RW, Parker JM, Lorber J, Crea R, Thibaudeau K. Nonhealing surgical wounds in a patient with plasminogen deficiency type 1 successfully treated with intravenous plasminogen: a case report. *Adv Skin Wound Care* 2024; **37**:387–391.

4 Nasiri A, Nassar M, Alzahrani H. Plasminogen deficiency: a case report and review. *Cureus* 2023; **15**:e45676.

5 Mehta R, Shapiro AD. Plasminogen deficiency. *Haemophilia* 2008; **14**: 1261–1268.

6 Rodríguez-Ares MT, Abdulkader I, Blanco A, Touriño-Peralba R, Ruiz-Ponte C, Vega A, Cameselle-Teijeiro J. Ligneous conjunctivitis: a clinicopathological, immunohistochemical, and genetic study including the treatment of two sisters with multiorgan involvement. *Virchows Arch* 2007; **451**:815–821.

7 Hangul M, Tuzuner AB, Somekh I, Klein C, Patiroglu T, Unal E, Kose M. Type 1 plasminogen deficiency with pulmonary involvement: novel treatment and novel mutation. *J Pediatr Hematol Oncol* 2021; **43**:e558–e560.

8 Shapiro AD, Nakar C, Parker JM, Thibaudeau K, Crea R, Sandset PM. Plasminogen, human-TVMH for the treatment of children and adults with plasminogen deficiency type 1. *Haemophilia* 2023; **29**:1556–1564.

9 Nakar C, Thukral N, McDaniel HL, Parker JM, Trybul D, Shapiro A. Acute airway obstruction in 4 pediatric patients with congenital plasminogen deficiency (C-PLGD) treated with intravenous plasminogen (human) replacement therapy under an expanded access protocol. *Blood* 2020; **136**:322.

10 Biesinger BS, Male C, Kranebitter V, Binder J, Niederle MB, Reinprecht A, Binder C. Persistent hydrocephalus, shunt, and subglottic stenosis in a newborn with plasminogen deficiency due to delayed treatment with plasminogen concentrates: a case report. *Neonatology* 2024; **121**: 266–270.

DOI:10.1097/MBC.0000000000001391

Danazol and cost-savings in immune thrombocytopenia and in immune thrombotic thrombocytopenic purpura

Mala Varma[a], Ilan Shapira[b], Mark Friedman[c,d], Ibrahim Nakhoul[a,e,f], Vamsee Torri[a,g], Jonah Shulman[b,h], Peter Kozuch[a], Bruce Culliney[b], Amit A. Patel[a,i,j,k], Joseph Yoe[a], Vijay P. Shah[l], Tahir Mirzoyev[a] and Maria Machuca[b]

[a]Hematology-Oncology, Mount Sinai West and Mount Sinai Morningside Hospitals, [b]Hematology-Oncology, Mount Sinai Beth Israel Medical Center, [c]Pathology/Blood Bank, Mount Sinai West and Mount Sinai Morningside Hospitals, [d]NYU Langone Hospital-Long Island, Mineola, New York NY, [e]Holston Valley Medical Center, [f]Indian Path Community Hospital, Kingsport, TN, [g]Saint Joseph's Hospital and Medical Center, Phoenix, AZ, [h]Mount Sinai Hospital, New York, NY, [i]RWJ Barnabas Health - Jersey City Medical Center, Jersey City, NJ, [j]St. George's University School of Medicine, St. George's, GD, [k]New York Institute of Technology and [l]Pathology/Blood Bank, Mount Sinai Beth Israel Medical Center, New York, NY, USA

Correspondence to Dr Mala Varma,
E-mail: varmala91@gmail.com

Received 8 September 2025 **Accepted** 16 September 2025

To the Editor,

Novel therapies for immune thrombocytopenia (ITP) and for immune thrombotic thrombocytopenic purpura (iTTP) are effective but expensive. Danazol, a mild attenuated androgen, has steroid-sparing activity in ITP [1] and reduces plasma exchange (PEX) requirement in relapsed/refractory iTTP [2,3]. We report the results of two prospective studies showing cost savings associated with danazol therapy in ITP and in iTTP. Both studies were approved by the institutional review board. All patients signed informed consent. The iTTP study was registered at ClinicalTrials.gov (ID# NCT00953771). Danazol is not FDA-approved for ITP nor for iTTP.

Starting in 2005 on our ITP study, patients with ITP and platelet count (PLT) less than 30 000/μl received danazol 600 mg oral (p.o.) daily in combination with anti-Rh(D) immune globulin 75 μg/kg intravenously (i.v.) on day 1, repeated whenever the PLT fell below 30 000/μl. After 1 year, danazol was reduced to 400 mg daily for 3 months then to 200 mg daily for 9 months. A comparison of the rate of discontinuation of anti-Rh(D) after 1 year (projected 38%) with that (18%) in historical controls treated with anti-Rh(D) alone [4] was planned. Twenty-six patients would allow for power 80%, α 0.10. Chi-square analysis was used to compare requirement for only a single infusion of anti-Rh(D) in each group. The Student's t-test was used to compare rate of anti-Rh(D) usage over time in both groups. Results were analyzed by intent-to-treat.

Study patients and historical controls were matched for number of patients (26, 28), percentage responders (92, 93), and median duration of follow-up (28.12 months, 26 months), respectively. Eight (31%) of 26 study patients required only a single anti-Rh(D) infusion, compared to 1 (3.6%) of 28 control patients, $P = 0.007$, 95% confidence interval (95% CI) -0.46 to -0.08. At 1 year of follow-up, there was a 16% reduction in anti-Rh(D) use in comparison with historical controls, with mean number of infusions per month 0.36 for study patients, compared to 0.43 for controls, $t = .8354$, $P > 0.05$. Toxicities were mild. One patient had a retroperitoneal bleed following an abdominal lymph node biopsy, despite having PLT 87 000/μl three days earlier.