



## BIBLIOGRAFÍA ENERO-FEBRERO 2025

Os presentamos los trabajos más relevantes publicados en el periodo de enero-febrero 2025, clasificados por ensayos clínicos (*clinical trials*), estudios en vida real (*real world evidence*), investigación básica (*research*) y artículos de revisión (*review*)

### CLINICAL TRIALS

**Cooper N, Jansen AJG, Bird R, Mayer J, Sholzberg M, Tarantino MD, Garg M, Ypma PF, McDonald V, Percy C, Košťál M, Goncalves I, Bogdanov LH, Gernsheimer TB, Diab R, Yao M, Daak A, Kuter DJ. Efficacy and Safety Results With Rilzabrutinib, an Oral Bruton Tyrosine Kinase Inhibitor, in Patients With Immune Thrombocytopenia: Phase 2 Part B Study. *Am J Hematol.* 2025 Mar;100(3):439-449.doi: 10.1002/ajh.27539. Epub 2025 Jan 22. PMID: 39844469; PMCID: PMC11803537.**

Current treatments for persistent or chronic immune thrombocytopenia (ITP) are limited by inadequate response, toxicity, and impaired quality of life. The Bruton tyrosine kinase inhibitor rilzabrutinib was evaluated to further characterize safety and durability of platelet response. LUNA2 Part B is a multicenter, phase 1/2 study in adults with ITP ( $\geq 3$  months duration, platelet count  $< 30 \times 10^9/L$ ) who failed  $\geq 1$  ITP therapy (NCT03395210, EudraCT 2017-004012-19). Oral rilzabrutinib 400 mg bid was given over 24 weeks, with optional long-term extension (LTE). Primary endpoints were safety and platelet counts  $\geq 50 \times 10^9/L$  on  $\geq 8$  of the last 12 weeks of main treatment without rescue medication. From 22 March 2018 to 31 January 2023, 26 patients were enrolled. Patients had baseline median platelet count  $13 \times 10^9/L$ , ITP duration 10.3 years, and six prior ITP therapies (46% splenectomized). Nine (35%) patients achieved the primary endpoint. Platelet counts  $\geq 50 \times 10^9/L$  or  $\geq 30 \times 10^9/L$  and doubling from baseline without rescue therapy were sustained for a mean 9.3 weeks. 11 (42%) LTE-eligible patients were ongoing with median LTE platelet  $> 80 \times 10^9/L$ . Three (12%) patients received rescue medication during main treatment, none in LTE. Clinically meaningful improvements were observed in fatigue and women's health. With a median treatment duration of 167 days (main treatment), 16 (62%) patients had  $\geq 1$  treatment-related adverse event (AE), mainly grade 1, including diarrhea (35%), headache (23%), and nausea (15%). There was no treatment-related grade  $\geq 2$  bleeding/thrombotic events/infections, serious AE, or death. Rilzabrutinib continues to demonstrate durable platelet responses with favorable safety profile in previously treated ITP patients. Trial Registration: NCT03395210

**Cooper N, Bussel JB, Kaźmierczak M, Miyakawa Y, Cluck S, Lledó García R, Haier B, Lavrov A, Singh P, Snipes R, Kuter DJ. Inhibition of FcRn with rozanolixizumab in adults with immune thrombocytopenia: Two randomised, double-blind, placebo-controlled phase 3 studies and their open-label extension. *Br J Haematol.* 2025 Feb;206(2):675-688. doi: 10.1111/bjh.19858. Epub 2024 Nov 18. PMID: 39552477; PMCID: PMC11829145.**

Primary immune thrombocytopenia (ITP) is an antiplatelet-antibody-mediated disorder with accelerated platelet clearance and decreased platelet production. Rozanolixizumab, a monoclonal IgG4 anti-FcRn antibody, blocks IgG recycling and decreases IgG levels. We report efficacy and safety of rozanolixizumab in adults with persistent/chronic ITP in 24-week phase 3 studies (TP0003; TP0006), and their 52-week open-label extension (OLE). Primary end-point was durable clinically meaningful platelet response (DCMPR) of  $\geq 50 \times 10^9/L$  for 8/12 weeks during Weeks 13-25 in the double-blind studies. Operational delays and evolving ITP treatment landscape led the sponsor to terminate these studies early; thus, only 21 and 12 (TP0003) and 20 and 10 (TP0006) patients were randomised to rozanolixizumab or placebo. Forty-three patients enrolled in the OLE: 42 started on every 2-week dosing; 21 later switched to weekly



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dosing. More rozanolixizumab-treated than placebo-treated patients achieved DCMPR: 4/21 versus 0 (TP0003) and 1/20 versus 0 (TP0006). Platelet increases to  $\geq 50 \times 10^9/L$  were observed on Day 8 in 52.4% (TP0003; 2/12 placebo) and 45.0% (TP0006; 1/10 placebo) of rozanolixizumab-treated patients. OLE platelet increases were maintained while on weekly dosing. The most frequent treatment-emergent adverse events overall were headache, pyrexia and nausea, as seen previously. Weekly dosing appears more efficacious than every 2-week dosing.

### REAL WORLD EVIDENCE

**Kang KW, Choi Y, Lim HJ, Kwak K, Choi YS, Park Y, Kim BS, Lee KS, Ahn KH. Impact of platelet transfusion and bleeding risk stratification in patients with immune thrombocytopenia before procedures. Sci Rep. 2025 Feb 12;15(1):5174. doi: 10.1038/s41598-025-89419-w. PMID: 39939729; PMCID: PMC11822007.**

The main treatment goal for immune thrombocytopenia (ITP) is bleeding risk reduction, particularly during procedures. While adjusting platelet thresholds with ITP treatments is recommended, platelet transfusions are commonly used despite controversial benefits. We evaluated the effectiveness of platelet transfusion in reducing post-procedure bleeding risk and identified predictive indicators of bleeding. A nationally representative database was used to develop a model predicting post-procedure bleeding risk in patients with ITP. Machine learning analyses, including random forest feature importance and Shapley additive explanations (SHAP) values, assessed 34 risk factors, including the platelet transfusion amount. The random forest model had an area under the receiver-operating characteristic curve of 93.6%. Key variables influencing bleeding risk included platelet transfusion amount, high-risk procedure, anticoagulant use, anemia, age, ITP treatment, and newly diagnosed ITP, all positively correlated with bleeding risk. Conversely, no antiplatelet or anticoagulant use and moderate- or low-risk procedures were negatively associated with bleeding risk. SHAP plots showed that platelet transfusion amount correlated with high-risk procedures, and bleeding risk increased with age in high-risk procedures. Bleeding risk in patients with ITP is primarily determined by procedural risk and patient condition, rather than platelet transfusion. Minimizing unnecessary platelet transfusions and addressing bleeding risk factors pre-procedure is crucial.

**Liang H, Duan L, Long M, Tie S, Sun C, Ma S, Wang J, Wang S. Analysis of Risk Factors and the Establishment of a Predictive Model for Thrombosis in Patients with Immune Thrombocytopenia. Clin Appl Thromb Hemost. 2025 Jan-Dec;31:10760296241301398. doi: 10.1177/10760296241301398. PMID: 39763222; PMCID: PMC11705361.**

**OBJECTIVES:** To explore the risk factors for thrombi occurring in patients with immune thrombocytopenia (ITP) and establish a risk prediction model to better predict the risk of thrombosis in patients with ITP.

**METHODS:** We retrospectively analyzed 350 ITP patients who had been hospitalized in the First People's Hospital of Yunnan Province between January 2024 and June 2024. For all patients, we recorded demographic characteristics and clinical data, analyzed the risk factors for thrombosis in ITP patients and then developed a risk prediction model.

**RESULTS:** Stepwise logistic regression analysis indicated that a high D-dimer level, a low PC (platelet count) and a high Padua score were independent risk factors for thrombosis in ITP patients. According to multivariate analysis, a predictive model for thrombus risk showed that the area; the area under the ROC curve (AUC) was 0.673 (95% CI: 0.615-0.730) and the maximum Youden index, sensitivity and specificity were 0.272, 47.0% and 80.2%,



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respectively. **CONCLUSION:** A high D-dimer level, low PC, and high Padua score were shown to be independent risk factors for thrombosis in ITP patients. Also, the study showed that these three risk factors might be used as a risk predictors for thrombosis in ITP patients to some extent.

### REVIEW

**Chowdhury SR, Sirolich E, Guyatt G, Gill D, Modi D, Venier LM, Mahamad S, Chowdhury MR, Eisa K, Beck CE, Breakey VR, de Wit K, Porter S, Webert KE, Cuker A, O'Connor C, DiRaimo JM, Yan JW, Manski C, Kelton JG, Kang M, Strachan G, Hassan Z, Pruitt B, Pai M, Grace RF, Paynter D, Charness J, Cooper N, Fein S, Agarwal A, Nazaryan H, Siddiqui I, Leong R, Pallapothu S, Wen A, Xu E, Liu B, Shafiee A, Rathod P, Kwon H, Dookie J, Zeraatkar D, Thabane L, Couban R, Arnold DM. Treatment of Critical Bleeds in Patients With Immune Thrombocytopenia: A Systematic Review. *Eur J Haematol.* 2025 Mar;114(3):458-468. doi: 10.1111/ejh.14351. Epub 2024 Nov 18. PMID: 39552264; PMCID: PMC11798764.**

**OBJECTIVES:** Evidence-based protocols for managing bleeding emergencies in patients with immune thrombocytopenia (ITP) are lacking. We conducted a systematic review of treatments for critical bleeding in patients with ITP.

**METHODS:** We included all study designs and extracted data in aggregate or individually for patients who received one or more interventions and for whom any of the following outcomes were reported: platelet count response, bleeding, disability, or death.

**RESULTS:** We identified 49 eligible studies reporting 112 critical bleed patients with ITP, including 66 children (median age, 10 years), 36 adults (median age, 41.5 years), and 10 patients with unreported age. Patients received corticosteroids (n = 67), IVIG (n = 49), platelet transfusions (n = 41), TPO-RAs (n = 17), and splenectomy (n = 28) either alone or in combination. Studies reported 29 different treatment combinations, the 5 most common were corticosteroids, platelet transfusion and splenectomy (n = 13), corticosteroids and IVIG (n = 13), or splenectomy alone (n = 13); IVIG alone (n = 11); and corticosteroids, IVIG and TPO-RA (n = 8). Mortality among patients with critical bleeds in ITP was 30.6% for adults and 19.7% for children.

**CONCLUSIONS:** The effects of individual treatments on patient outcomes were uncertain due to very low-quality evidence. There is a need for a standardized approach to the treatment of ITP critical bleeds. **SYSTEMATIC REVIEW REGISTRATION:** CRD42020161206.

**Zheng Z, Liu J, Yun M, Deng L, Xiang P, Jiang M, Wang R, Liu C. Immune thrombocytopenia in patients with systemic lupus erythematosus. *Clin Rheumatol.* 2025 Jan;44(1):97-104. doi: 10.1007/s10067-024-07235-5. Epub 2024 Dec 4. PMID: 39627479.**

Immune thrombocytopenia (ITP) is a common hematological manifestation of systemic lupus erythematosus (SLE). The diversity of its clinical features and treatment responses may reveal the complex pathophysiological mechanisms of the disease. To enhance the therapeutic response rate and improve the prognosis for SLE patients with concurrent ITP, while reducing adverse events during the treatment process, it is crucial to accurately identify and apply clinical parameters to predict patients' responses to treatment. In addition to conventional therapeutic approaches such as glucocorticoids, immunosuppressants, and intravenous immunoglobulin (IVIG), a range of emerging therapies are gradually becoming the focus of research. These innovative therapeutic strategies include thrombopoietin receptor agonists (TPO-RAs), targeted therapies against B-cells, and plasma cell-targeted treatments. With a deepening understanding



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of the role of platelets in immune and inflammatory responses, novel platelet-targeted therapeutic agents in the field of SLE-ITP treatment may demonstrate significant potential. Despite this, to ensure the clinical efficacy and safety of these therapeutic approaches, we must rely on rigorously designed randomized controlled trials (RCTs) for further validation. This article provides a systematic review of the pathogenesis of systemic lupus erythematosus (SLE) complicated by immune thrombocytopenia (ITP) and conducts a comprehensive overview of current treatment strategies. The article also provides an in-depth exploration of the key biomarkers that may influence the therapeutic response in SLE-ITP patients. This comprehensive analysis aims to elucidate the factors that potentially affect the efficacy of treatments and contribute to a more personalized approach to patient care.

### RESEARCH

**Radwan RA, Elsalakawy WA, Abdelaziz DM, Abdelrazek DM, Radwan SM. Bsm1, Apal and Fok1 variants of vitamin D receptor gene polymorphism as predictors of response to treatment in immune thrombocytopenia patients. Mol Cell Biochem. 2025 Mar;480(3):1919-1929. doi: 10.1007/s11010-024-05100-2. Epub 2024 Sep 23. PMID: 39312029.**

Vitamin D receptor (VDR) polymorphisms are linked with the incidence and severity of several autoimmune diseases. The current work aimed at evaluating if VDR rs1544410 (Bsm1), rs7975232 (Apal) and rs2228570 (Fok1) gene polymorphisms could be predictors of response to steroid treatment in patients with immune thrombocytopenia (ITP). The study involved 75 steroid treatment responders and 75 resistant ITP patients. All participants were subjected to VDR Bsm1, Apal and Fok1 gene polymorphisms analysis through genotyping by RT-PCR. Carrying the Fok1 F allele was significantly associated with low vitamin D level and increased risk of developing steroid resistance. Interestingly, the tri-allelic haplotypes BAF and BaF were significantly only present in steroid resistant ITP patients. Thus, the present study suggests that VDR Fok1 F allele may contribute to ITP pathogenesis and resistance to steroid treatment. Knowing the genetic background of patients helps to individualize treatment to obtain a better outcome.

**Fattizzo B, Marchetti A, Bosi A, Gurnari C, Giannotta JA, Pedone GL, Rossi E, Carrai V, Guido A, Brioschi F, Carpenedo M, Crugnola M, Caramazza D, Leuzzi L, Marchetti M, Merati G, Malato S, Vianello F, Patriarca A, Awada H, Bortolotti M, Canzi M, Bolli N, Capecchi M, Chen F, Artoni A, Maciejewski JP, Barcellini W. Clonal hematopoiesis in patients with autoimmune thrombocytopenia: an international multicenter study. Blood Adv. 2025 Feb 11;9(3):488-495. doi:10.1182/bloodadvances.2024014984. PMID: 39536292; PMCID: PMC11814519.**

Diagnostic boundaries between immune thrombocytopenia (ITP) and other thrombocytopenic states, such as thrombocytopenic myelodysplastic syndromes, may be difficult to establish, and the detection of somatic mutations by next-generation sequencing (NGS) may be of aid. Here, we aimed at characterizing the prevalence and clinical significance of clonal hematopoiesis in ITP. In this multicentric retrospective observational study, we enrolled 167 adult patients with ITP, followed at 13 centers in Italy, United Kingdom, and the United States. Patients underwent NGS evaluation after a median of 3.6 years from ITP onset, and 83% had received at least 1 therapy line, for a median of 2 lines (range, 0-9); 51 of 167 patients (30%) had at least 1 mutation. After exclusion of germ line variants and polymorphisms, 31 of 167 (18.5%) were defined as having clonal hemopoiesis. Most commonly mutated genes were TET2, DNMT3A,



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SRSF2, and ASXL1 (median variant allele frequency, 29%); 19 of 31 patients (68%) had high-risk variants, and 8 had multiple mutations. Mutated patients were more frequently older males and showed a shorter time from first to second-line therapy, particularly with thrombopoietin receptor agonist (TPO-RA). Additionally, clonal hematopoiesis was associated with increased thrombotic risk (26% vs 8% in NGS-negative cases;  $P = .01$ ), independently from TPO-RA exposure, though with an age effect. These data demonstrated the prevalence of clonal hematopoiesis in 18% of adult patients with ITP, which is associated with older age, relapsed/refractory disease, and high risk of thrombotic complications.