Ethnicity affects relapse-free survival in immune-mediated thrombotic thrombocytopenic purpura

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Received: August 7, 2025.
Accepted: December 15, 2025.
Early view: January 8, 2026.

https://doi.org/10.3324/haematol.2025.288789

Supplementary Methods

Patients

Diagnosis of iTTP required findings of thrombotic microangiopathy with ADAMTS13 activity <10% and anti-ADAMT13 IgG titers ≥15U/mL. Besides the risk of excess of infectious complications, 7 patients with an uncontrolled HIV infection were not included here as their response to rituximab could have differed from this of HIV-negative patients.

Treatment and response

Treatment of iTTP in the acute phase was based on current national and international guidelines (1–3). Since October 2000, acute phase treatment consisted of daily therapeutic plasma exchange started at diagnosis and carried out until clinical remission. Patients received glucocorticoids (1 mg/kg/day, for a maximum of 3 weeks) unless contraindicated. Caplacizumab became available in France in September 2018 and it was used based on the registrational trials and the international and national recommendations in acute phase iTTP. In the acute phase, rituximab was routinely used from 2005; it was administered intravenously at a dose of 375mg/m^2 on a day-1-4-8-15 schedule and referred to as "rituximab-containing regimens". In the preemptive setting, rituximab was used systematically by 2007, and started after detection of ADAMTS13 deficiency (<10%). The dose and administration regimen of rituximab was usually of 375 mg/m^2/week for 4 weeks until 2012; thereafter, one single administration of 375 mg/m^2 was performed. (4) ADAMTS13 monitoring was performed at least weekly until ADAMTS13 improvement (i.e., ≥20%) in the acute setting, and at least monthly in the preemptive setting; after normalization, ADAMTS13 activity was measured usually in every 3 months.

Clinical response and remission, and relapse definitions were based on previous studies. Briefly, clinical response occurred in patients when platelet count recovered durably. Complete or partial remission was defined by a partial (activity ≥20% but <50%) or complete (activity ≥20%) ADAMTS13 recovery in a patient with clinical response. Relapse was defined as a new episode in patients who had formerly reached remission, or following a 30-day period with no further TPE and caplacizumab. ADAMTS13 relapse was defined as ADAMTS13 activity below 20% with at least two consecutive measurements. (4,5)

Statistical analysis

Descriptive statistics were performed on the overall cohort and stratified by ethnic groups. Continuous variables were summarized as medians with interquartile ranges (IQR, 25–75%) and compared using the Wilcoxon–Mann–Whitney test. Categorical variables were described as counts and percentages and compared using chi-squared or Fisher's exact tests, as appropriate.

All statistical analyses were conducted using R version 4.4.2 for macOS® (https://www.r-project.org, accessed October 2024), using the packages survival, survminer, coxme, ggplot2, and gtsummary. All p-values were two-sided, with a significance threshold set at $p < 0.05$.

ADAMTS13 activity recovery was analyzed using a time-to-event approach. Kaplan–Meier estimates were used to assess the cumulative incidence of ADAMTS13 recovery over time. Relapse-free survival was also analyzed using Kaplan–Meier curves, stratified by ethnicity and episode sequence. Time-to-event was defined as the interval from rituximab administration to the occurrence of the first or any subsequent relapse. Group comparisons were performed using log-rank tests. The number at risk was displayed below each survival curve.

Multivariable models were developed to identify factors associated with relapse, incorporating patient-level covariates including age, sex, indication for rituximab, episode type (first or relapsing), and ethnicity. To account for recurrent events, a Prentice–Williams–Peterson (PWP) model was used, stratified by episode number and clustered on patient identifiers. Mean cumulative function (MCF) curves were generated to visualize the average number of relapses over time, stratified by ethnicity. Given that missing data accounted for less than 10%, analysis was performed on a complete-case basis.

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