Poster 3773

Cognitive Impairment Among Patients With Chronic Immune Thrombocytopenia

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BACKGROUND

- Immune thrombocytopenia (ITP) is an autoimmune disease associated with autoantibody-mediated platelet destruction and impaired platelet production, resulting in thrombocytopenia and high bleeding risk[1,2]
- Fatigue and impairment of both memory and concentration are observed in ITP, along with microbleeds in patients with lower platelet counts. This is hypothesized to arise from acute neural inflammation and thrombotic occlusions of small blood vessels in the brain[3-6]
- Understanding the effect of chronic ITP on brain function will be improved by estimates of prevalence, nature, and severity of cognitive impairment in patients with this condition
- **Aim of this analysis**: To assess the cognitive impairment in difficult-to-treat patients with ITP

METHODS

- Participants (N=60) who were enrolled in Part A of a global phase 1/2 study (NCT03395210) assessing the safety and efficacy of the Bruton tyrosine kinase inhibitor rilzabrutinib in ITP underwent cognitive assessment at the pre-treatment baseline assessment (prior to rilzabrutinib treatment)
- Cognition was assessed using the Cogstate Brief Battery (CBB). Individual tests from the CBB, and composite scores from these tests, have a high sensitivity to cognitive dysfunction in clinical trial contexts (**Table 1**)[7,8]

Psychomotor function was measured using the Detection test (DET)

Visual attention was measured using the Identification test (IDN)

Visual learning was measured using the One Card Learning test (OCL)

Working memory was assessed with the One Back test (ONB)

Table 1. Outcome Measures of Cogstate Tests

Test or Composite	Main Cognitive Function Measured	Cognitive Domain	Primary Performance Measure	Direction of Scores for Better Performance
Individual Tests				
Detection Test (DET)*	Psychomotor function	Attention	Speed of performance; mean of the log10 transformed reaction times for correct responses	Lower score = better performance
Identification Test (IDN)*	Attention	Attention	Speed of performance; mean of the log10 transformed reaction times for correct responses	Lower score = better performance
One Card Learning Test (OCL)	Visual learning	Memory and learning	Accuracy of performance; arcsine transformation of the square root of the proportion of correct responses	Higher score = better performance
One Back Test (ONB)	Working memory	Executive function	Accuracy of performance; arcsine transformation of the square root of the proportion of correct responses	Higher score = better performance
Composite Scores				
Psychomotor function/ attention	Rapid and automatic decisions	Attention	Combination of age standardized scores on the DET and IDN, re-standardized against population norms	Higher score = better performance
Learning/ working memory	Accurate and careful decision making	Higher cognitive function	Combination of age standardized scores on the OCL and ONB, re-standardized against population norms	Higher score = better performance

*Indicates the sign of standardized scores is reversed so that negative standard scores indicate performance below normal mean (and vice versa).

- For each participant, prior to rilzabrutinib treatment, the score on each test was compared with age-matched normative data to produce a standardized score (Z-score)[7]
  - Z-scores measure the distance between an observed value and a reference mean using standard deviation units and can be positive or negative, indicating that the observed value lies above or below the mean, respectively
  - Z-scores of ≤ -1 were categorized as having an impairment
- Descriptive summary statistics, including mean Z-scores for individual tests and composite cognitive scores (psychomotor/attention, learning/memory), and level of impairment are presented
- Relationships between cognitive impairment and demographics, concomitant medication, and medical history were also explored

RESULTS

BASELINE DEMOGRAPHICS AND PRIOR TREATMENT

- 49 patients with baseline assessments had a mean age of 50 y, 57% were female, and 71% had an ITP duration of ≥3 y (**Table 2**)
- Medical history included hypertension (n=17), depression/anxiety (n=8), diabetes (n=7), and stroke/central nervous system bleeding (n=1)
- 14 patients each had concomitant corticosteroids or thrombopoietin receptor agonists (TPO-RA), and 7 patients had both concomitant therapies

Table 2. Baseline Patient Demographics and Prior Treatment History

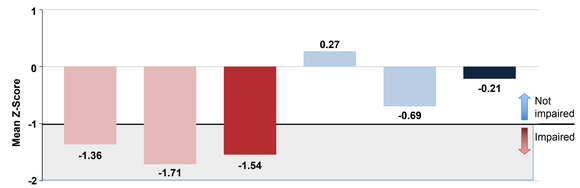
Baseline Characteristics	Patients (N=49)
Mean age, y (SD)	50 (13)
Gender, n (%)	
Female	28 (57)
Male	21 (43)
Baseline platelet count, n (%)	
≤15×10⁹/L	27 (55)
>15×10⁹/L	22 (45)
Duration of ITP ≥3 y, n (%)	35 (71)
Prior medication, n (%)	
Corticosteroids	47 (96)
TPO-RA	38 (78)
Prior splenectomy, n (%)	14 (29)

COGNITION

- Group mean Z-scores on the tests for psychomotor function (DET), attention (IDN), and working memory (ONB) were all negative (**Figure 1**)
- The magnitude of negative performance on the detection and identification tests indicated moderate impairment in psychomotor and attentional functions
- Performance on the working memory test indicated mild impairment
- Performance on the visual learning test was close to normal

Figure 1. Clinically Important Impairment in Psychomotor Function and Attention in ITP Patients

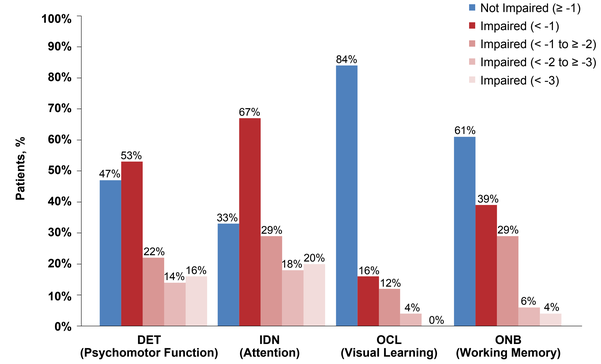
	Detection Test (DET)	Identification Test (IDN)	Psychomotor/ Attention (DET, IDN)*	One Card Learning (OCL)	One Back Test (ONB)	Learning/ Memory Score (OCL, ONB)*
Mean Z-Score (SD)	-1.36 (1.36)	-1.71 (1.56)	-1.54 (1.40)	0.27 (1.18)	-0.69 (1.27)	-0.21 (0.98)
95% CI	-1.75, -0.97	-2.16, -1.26	-1.94, -1.13	-0.07, 0.61	-1.05, -0.33	-0.49, 0.07
Min, Max	-4.14, 1.12	-4.94, 1.43	-4.52, 1.27	-2.60, 2.54	-4.43, 1.83	-3.51, 1.29



*For summaries of composite scores, the mean (DET, IDN) was used for psychomotor/attention and mean (OCL, ONB) for learning/memory, respectively.

- Cognitive impairment levels were highest for attention (IDN: 67%), followed by psychomotor function (DET: 53%), working memory (ONB: 39%), and visual learning (OCL: 16%) tests (**Figure 2**)
- Psychomotor/attention impairment was greater (DET, IDN: 69%) than learning/memory (OCL, ONB: 43%)

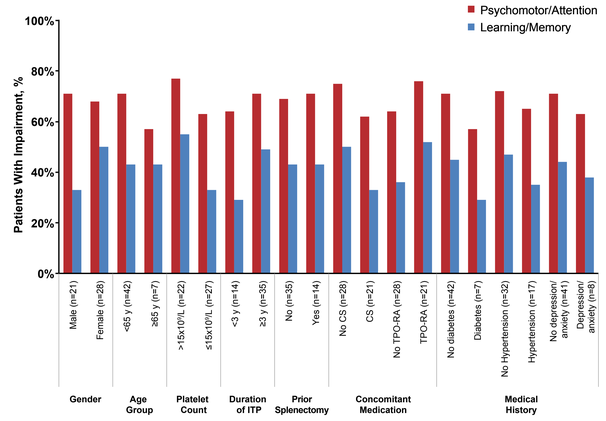
Figure 2. Rate of Clinically Important Cognitive Impairment in Individual Patients With ITP



DET, Detection Test; IDN, Identification Test; OCL, One Card Learning; ONB, One Back Test.

- Cognitive deficits occurred irrespective of baseline biological/clinical characteristics (**Figure 3**)
- The percentage of participants with psychomotor/attention cognitive impairment was consistently higher than those with learning/memory impairment
- No significant differences comparing percent impaired between the different variables and cognitive impairment were found. This could be due to low statistical power/small sample size

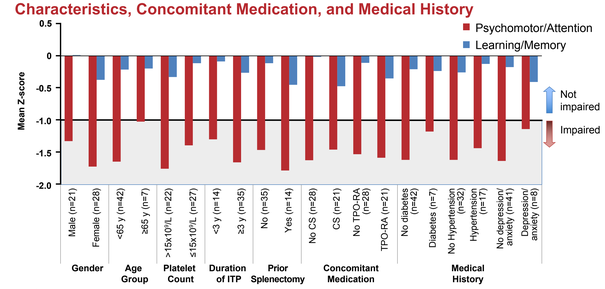
Figure 3. Cognition Data by Biological and Clinical Characteristics in Patients With Baseline CBB Assessments



Note: Only 1 patient had a stroke/central nervous system bleeding, so this category is not included here.
CBB, Cogstate Brief Battery; CS, corticosteroids; TPO-RA, thrombopoietin receptor agonists.

- The level of impairment was substantial for the psychomotor function/attention tests irrespective of baseline biological/clinical characteristics (**Figure 4**)

Figure 4. Severity of Cognitive Deficit Based on Baseline Characteristics, Concomitant Medication, and Medical History



Note: Only 1 patient had a stroke/central nervous system bleeding, so this category is not included here.
CS, corticosteroids; TPO-RA, thrombopoietin receptor agonists.

CONCLUSIONS

- This report provides evidence of cognitive impairment in patients with ITP
- Cognitive impairment was moderate in magnitude for psychomotor/attention, and mild for learning/memory
- When considered as a population, patients with difficult-to-treat ITP show clinically important impairment in attentional functions
- When considered individually, clinically important cognitive impairment occurs in ~50% of ITP patients, manifesting mainly in attentional functions
- Cognitive impairment was not related to medication history or other clinical characteristics
- From the perspective of magnitude alone, impairment in attentional function observed in ITP patients was equivalent or greater in magnitude to that observed in patients of similar age with mild traumatic brain injury[7], moderate-severe depressive disorder[9], or chronic fatigue syndrome[10]
- In the context of cerebrovascular disease, the nature and magnitude of impairment observed in the ITP group would be consistent with the clinical classification of vascular cognitive disorders[11]
- Cognitive impairment in the current ITP patient sample warrants further clinical investigation

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LK and KM: nothing to disclose

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