Zuberitamab, an innovative anti-CD20 monoclonal antibody, for patients with primary immune thrombocytopenia in China: a randomized, double-blind, placebo-controlled, phase 2 study

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Summary

Background Primary immune thrombocytopenia (ITP) is an autoimmune disease, and rituximab (RTX) induces long-term effect as second-line treatments. Zuberitamab is an innovative anti-CD20 monoclonal antibody, which was first developed in China and launched in diffuse large B lymphoma. This study aimed to investigate the safety, efficacy, and anticipated therapeutic dose of zuberitamab in Chinese ITP patients.

Methods This randomised, double-blind, placebo-controlled, phase 2 study was conducted at 26 hospitals in China. Eligible patients were aged 18–70 years, had primary immune thrombocytopenia for more than 6 months, and did not respond or relapsed after previous treatment and had a pre-treatment platelet count of $<30 \times 10^9$/L. Patients randomly received zuberitamab in a dose escalation (100/300/600 mg) or placebo once-weekly for 4 weeks and followed up to 24 weeks. The primary endpoint is the proportion of patients with a platelet count $\geq 50 \times 10^9$/L at week 8. Secondary endpoints include the proportion of patients with platelet counts $\geq 50 \times 10^9$/L or $\geq 100 \times 10^9$/L at least once within week 12/24, the proportion of patients experiencing platelets increased twice more than baseline as well as $\geq 30 \times 10^9$/L at least once during the treatment. Adverse events, pharmacokinetic, B cell depletion and immunogenicity were also assessed. This study is registered with https://www.chictr.org.cn/as ChiCTR2100050513.

Findings From October 2021 to March 2023, 50 patients were screened for eligibility, of whom 32 patients were enrolled and randomly assigned to placebo (n = 4), zuberitamab 100 mg (n = 10), 300 mg (n = 8) and 600 mg (n = 10) groups. The primary endpoint (PLT $\geq 50 \times 10^9$/L at week 8) was achieved by 40% of patients in the 100 mg group, while none in the other groups. Within 12 weeks, the proportions of patients in each treatment group achieving at least one instance of platelet count $\geq 50 \times 10^9$/L or $\geq 100 \times 10^9$/L or an increase twice more than baseline as well as $\geq 30 \times 10^9$/L were (70%, 38%, 50%), (60%, 13%, 30%), and (80%, 50%, 70%) in zuberitamab 100/300/600 mg groups,

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respectively. By week 24, the proportions of patients achieving these secondary endpoints remained relatively stable or showed a mild increase of around 10%. The anticipated therapeutic dose of zuberitamab was 100 mg. The plasma concentration of zuberitamab showed an increasing trend with dose (100 mg–600 mg) and linear pharmacokinetic behavior. CD19+ B cells and CD20+ B lymphocytes rapidly declined to 0% within one week and consistently maintained reduced levels throughout the entire treatment phase in three groups. Adverse events occurred in all patients with most of them were mild to moderate, no severe infections occurred. A slight decrease in immunoglobulins was observed in the 600 mg group, but gradually recovered at week 20. Three patients (2 in 100 mg and 1 in 600 mg group) were tested positive for anti-zuberitamab antibodies. We also observed that women, disease duration <12 months, and MAIPA + patients may have higher response rates.

Interpretation This study preliminarily confirmed that 100 mg zuberitamab was safe and effective in treating ITP and was recommended to support further investigation.

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Keywords: Immune thrombocytopenia; Zuberitamab; Rituximab; Safety and efficacy

Research in context

Evidence before this study

We searched PubMed on January 5, 2024, for clinical trials on the treatment of patients with immune thrombocytopenia, without language, study type, or date restrictions. The search terms used were "immune thrombocytopenia" [Title/Abstract] or "ITP" [Title/Abstract] and "rituximab" [Title/Abstract] or "CD20 monoclonal antibody" [Title/Abstract]. More than 20 prospective clinical trials on rituximab for ITP were identified, with only four studies conducted in Asian populations and three specifically in Chinese populations. In addition, novel CD20 monoclonal antibody drugs such as Rixathon™ and Truxima™, have obtained approval from French authorities, they have replaced the reference product in the majority of French hospitals for all indications, including ITP. However, the actual efficacy of this class of drugs in ITP lacks comprehensive assessment due to a dearth of prospective clinical trial results.

We also search on ClinicalTrials.gov using the terms "immune thrombocytopenia" or "ITP," "recruitment," "adults," "anti-CD20 monoclonal antibody," yielded four clinical trials. One of these trials is intending to evaluate belimumab in combination with rituximab or placebo. The remaining three trials are prospective clinical studies investigating various CD20 monoclonal antibodies. Thus, we stand at the forefront of clinical trials exploring novel CD20 monoclonal antibody drugs in ITP.

Added value of this study

Rituximab exhibited an initial response rate of 40%–60% and stands out among second-line treatments. However, the widespread utilization of rituximab is hindered by its high cost. Zuberitamab, an innovative anti-CD20 monoclonal antibody, was initially developed in China and recently introduced for treating diffuse large B lymphoma. With heightened binding activity to B cells, it swiftly and thoroughly eradicates them. This randomized, double-blind, placebo-controlled phase 2 study found that zuberitamab was excellent tolerability, encouraging response rates of 40%–80% were observed within week 24 with 100 mg, no severe infections were observed. The depletion of circulating B cells was rapid, occurring within 1 week, and profound, with B-cell counts remaining low in the peripheral blood for at least 24 weeks. These results suggest that Zuberitamab exhibits favorable efficacy and safety in Chinese ITP patients.

Implications of all the available evidence

This study provides evidence that Zuberitamab could be an effective treatment option for Chinese ITP patients. The dose of 100 mg was recommended to support further investigation. This study enhances the assessment of the efficacy and safety of CD20 monoclonal antibodies in the Chinese ITP patients. It also represents the first prospective double-blind trial to evaluate innovative CD20 monoclonal antibody drugs in ITP. Furthermore, expanding the indications for Zuberitamab holds promise in alleviating the economic burden on ITP patients in China.

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by a dual pathology involving augmented platelet destruction and impaired platelet production.[1,2] Corticosteroids and intravenous immunoglobulin are endorsed as primary interventions for ITP. Although the initial response rates with corticosteroids range from 70% to 80%, two-thirds of ITP

patients exhibit relapse, resulting in a low long-term remission rate.[3] Moreover, a subset of ITP patients experiences relapse and necessitates additional therapy following one or more treatment strategies.[4] Because of the implication of B cells and auto-antibodies in the pathophysiology, anti-CD20 monoclonal antibodies such as rituximab (RTX) have become a valid second-line treatment option for ITP and are now recommended in most international guidelines.[1,2,5] RTX exhibits the longest duration of efficacy after treatment withdrawal, enabling sustained platelet levels in certain patients without the need for additional interventions, thereby significantly enhancing quality of life.[6,7] Over the past decades, clinical studies on RTX have demonstrated an initial response rate of 40%–60%, a 5-year sustained response rate of 20%–30%, and a median time to response (TTR) of 5.5 weeks in ITP.[6–9]

Notably, the economic considerations in treatment remain pivotal. Traditional rituximab dosing would entail substantial costs.[10] The elevated cost restricts the utilization of this drug among patients lacking robust economic support. In developing countries, financial constraints present a hurdle for the widespread accessibility of rituximab to a large cohort of underserved patients.[11] The emergence of drugs with same target as rituximab offers the prospect of significant savings to the healthcare system. Two such drugs, Rixathon™ and Truxima™, obtained approval from French authorities following rigorous preclinical assessments and large randomized controlled trials encompassing patients with follicular lymphoma and rheumatoid arthritis.[12,13] They have replaced the reference product in the majority of French hospitals for all indications, including ITP.[14] However, the efficacy and safety of these drugs for treating ITP have not been assessed in any prospective randomized study.[14] The therapeutic indications outlined in the drug labels of both RTX and its pharmacological counterparts do not encompass ITP, and were not approved by the National Medical Products Administration, presenting a reimbursement challenge for Chinese patients under medical insurance coverage.

Zuberitamab is an innovative anti-CD20 monoclonal antibody injection, which was developed by Zhejiang Bioray Biopharmaceutical Co. Ltd. (Zhe-jiang, China) with independent intellectual property rights. This drug was approved by the Chinese National Medical Products Administration and was recently launched in diffuse large B lymphoma (https://www.nmpa.gov.cn/yaowen/ypjgyw/ypyw/20230517152922112). Zuberitamab includes two heavy chains containing 451 amino acids and two light chains containing 213 amino acids, of which 26 amino acids are different from Rituximab (heavy chain: 16 amino acids in the variable region and 1 amino acid in the constant region; light chain: 9 amino acids in the variable region and the same constant region). In vitro pharmacodynamic results showed that zuberitamab has higher binding activity with B cells and the relative activity of antibody-dependent cell-mediated cytotoxicity (ADCC) was stronger than that of rituximab. Therefore, it could cause rapid and deep clearance of B cells (unpublished data). In the early stage, it showed similar efficacy and safety compared with rituximab in diffuse large B lymphoma, while zuberitamab has longer sustained complete response after drug withdrawal (unpublished data). Recently, it has been successfully incorporated into the national basic medical insurance in China, encompassing the expenses for combined treatment of diffuse large B-cell lymphoma.

Hence, our objective is to conduct an initial evaluation of the effectiveness and safety of the innovative anti-CD20 monoclonal antibodies and explore the optimal dosage in Chinese adult ITP patients for further clinical trials. Additionally, we aspire to secure inclusion of zuberitamab in ITP indications and medical insurance, thereby alleviating the financial burden on Chinese patients.

Methods

Study design and participants

This randomised, double-blind, placebo-controlled, phase 2 study was conducted from October 2021 to March 2023 at 26 hospital sites across China (Supplementary Table S1). The diagnosis of ITP was based on the established practice guidelines.[1,5] The study obtained approval from the ethics committees of all participating hospitals. In accordance with the Helsinki Declaration, informed consent was obtained from each patient before enrolment.

The inclusion criteria were as follows: patients aged 18–70 years, a ≥6-month history of ITP, did not respond or relapsed after previous treatment and without splenectomy; had two consecutive platelet counts (interval of >24 h) of less than 30×10^9/L during screening; haemoglobin ≥90 g/L; neutrophils ≥1.5×10^9/L; serum creatinine concentration of 1.5 times the upper limit of normal (ULN) or less; creatinine clearance of ≥60 ml/min; total bilirubin, alanine aminotransferase, and aspartate aminotransferase of 1.5 times the ULN or less; and an international normalised ratio and activated partial thromboplastin time not exceeding more than 20% the normal range. Bone marrow examination supports diagnosis of primary ITP (all patients underwent bone marrow examination to exclude myelofibrosis or other platelet-depleting disorders). Patients had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1 and a World Health Organization (WHO) bleeding grade of 0–1 with no need for rescue treatment within 2 weeks before assignment. Patients undergoing glucocorticoid therapy must maintain a stable dose for a minimum of 2 weeks prior to the initial administration. For patients receiving dapsone/sulfasalazine/cyclosporine A/mycophenolate

mofetil, a stable dose must be maintained for at least 3 months before the first infusion was administered. Patients with a history of receiving monoclonal antibodies with therapeutic effects in ITP, including but not limited to CD20 monoclonal antibodies, should have achieved sustained efficacy for at least six months. Additionally, cessation of monoclonal antibody treatment should have occurred at least one year ago, or there should be evidence of B-cell recovery. Patients of childbearing age were required to agree to use effective contraception during the study and within 12 months after study drug administration. Exclusion criteria included secondary ITP, drug-induced thrombocytopenia, virus-induced thrombocytopenia (e.g., HIV, hepatitis B or C virus), severe dysfunction of the heart, kidneys, liver, or lungs, severe immunodeficiency, pregnancy or breastfeeding, and myelofibrosis. Those who have been allergic to any ingredients in rituximab (or investigational drugs) in the past (more detailed exclusion criterias were presented in the Supplementary Material).

Randomisation and masking

In this randomized double-blind placebo-controlled trial, a non-blind statistician operated to generate a project random table, and automatically assigned random numbers to qualified subjects and the grouped trial drugs corresponding to the random numbers by Interactive Web Response System (IWRS). This is a stratified blocked randomization trial with a randomization ratio of 2: 2: 2: 1 (100 mg group: 300 mg group: 600 mg group: placebo). In order to maintain the balance of the groups at baseline, the course of disease (persistent vs. chronic) was taken as the stratification factor. Placebo was a blank liquid in the same package. Patients, investigators, and the sponsor were masked to treatment allocation during the 24-week double-blind period and allocation concealment was performed. Data collection was carried out by an independent follow-up board. Data analyses were performed by a third-party statistical team (Nanjing Yike Baoda Pharmaceutical Technology, Nanjing, China.). Outcome assessment was done by independent masked experts from Wuhan Union Hospital.

Procedures

Eligible participants were randomly assigned into four groups: 100/300/600 mg dose of zuberitamab or placebo. All subjects received once-weekly dosing for a total of 4 weeks with follow-up extended to 24 weeks. Antipyretics, analgesics or antihistamines were routinely used before intravenous infusion to prevent infusion-related reactions (glucocorticoids were prohibited). Dose modifications were not allowed during treatment. Patients who had treatment-related treatment-emergent adverse events as specified in the protocol could interrupt treatment at investigator's discretion (Criteria for trial suspension or termination were presented in the Supplementary Materials). Throughout the treatment period, the use of any agents explicitly indicated for treating ITP, including traditional Chinese medicine with anti-platelet effects, and anticoagulant/antiplatelet drugs was prohibited, except for rescue treatment to elevate platelets and concurrent ITP background therapy. Rescue medications were administered when there was sever bleeding, or when considered medically necessary by the investigator. The permitted rescue medications were IVIG, platelet transfusions.

Adverse events were evaluated from the first dose until 24 weeks. Platelet counts were monitored weekly in the first 8 weeks and then biweekly until 24 weeks. For pharmacokinetic analyses, plasma samples were collected within 2 h before drug administration on days 0, 7, 14, and 5 min after drug administration on days 0 and 21, then collected weekly from week 4 to week 8. Pharmacodynamic observation time points were the same as pharmacokinetics, but weekly monitoring continues for 24 weeks. Anti-drug antibody and neutralizing antibody were assessed on day 0, week 3, week 8, last visit or early withdrawal from the visit.

Outcomes

The primary objectives were to assess safety and efficacy of zuberitamab in patients with persistent or chronic ITP who have failed to prior treatment. The secondary objectives were to assess the pharmacokinetics, immunogenicity, pharmacodynamics and to explore recommended phase III dosing regimens.

The primary endpoint was the proportion of patients with a platelet count $\geq 50 \times 10^9$/L at week 8. Secondary endpoints included the proportion of patients with platelet counts $\geq 50 \times 10^9$/L or $\geq 100 \times 10^9$/L at least once within week 12/24, the proportion of patients experiencing platelets increased twice more than baseline as well as $\geq 30 \times 10^9$/L at least once during the treatment, the proportion of patients achieving treatment goals within week 12/24 (concomitant treatment reduction accompanied by reduced bleeding scores), and the proportion of patients who received rescue treatment within week 12/24. The duration of efficacy, pharmacokinetic and B cell depletion was also assessed. Adverse events are classified and assessed according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.

Statistical analysis

Efficacy analyses were conducted within the Full Analysis Set, encompassing patients who had screened and randomized successfully. Safety analyses were conducted within the safety set. Descriptive statistics were employed to summarize demographic characteristics.

Continuous variables were presented as median and interquartile range (IQR), and categorical variables were

presented as numbers (%). Unless otherwise stated, hypothesis testing will use two-sided tests, with 0.05 as the test level. Group differences for primary endpoint and categorical secondary endpoints were compared using Fisher's exact test. In the presence of missing data for efficacy analysis, it was considered as MNAR (missing not at random) and non-response was employed for interpolation or analysis. Data management and statistical analyses were performed using SAS version 9.4. A p-value less than 0.05 was considered statistically significant.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Patients and disposition

From October 2021 to March 2023, 50 patients were enrolled, and 18 patients were excluded due to failure to meet inclusion criteria. 32 patients randomized assigned into 4 groups: placebo (n = 4), zuberitamab 100 mg (n = 10), zuberitamab 300 mg (n = 8), and zuberitamab 600 mg (n = 10). All patients had received the drugs at least once in this study. One patient in the 300 mg group received only 3 injections, and the other patients all received 4 complete treatments. But 2 patients in the placebo group, 4 patients in the 100 mg group, 4 patients in 300 mg group, and 7 patients in 600 mg group withdrew prematurely from the trial during the follow-up period due to issues such as poor compliance, investigator decisions, or voluntary withdrawal (Fig. 1). The demographic and baseline characteristics of four groups are summarized in Table 1. The median age was 38 (29–52), 53 (28–64), 53 (29–60), and 34 (26–47) years for the placebo, zuberitamab 100/300/600 mg group, respectively. And the proportion of female patients in each group was 75%, 80%, 63%, and 60%, respectively. The baseline platelet counts were 15 (8–25) $\times 10^9$/L, 15 (14–23) $\times 10^9$/L, 9 (5–25) $\times 10^9$/L, and 11 (7–21) $\times 10^9$/L for the respective groups. All patients have received at least one type of prior treatment. Regarding comorbidities, aside from one patient in the zuberitamab 100 mg group who did not exhibit additional complications apart from ITP, all other patients presented with various comorbidities. Metabolic diseases were the most common, followed by hepatobiliary system diseases. Modified monoclonal antibody-specific immobilization of platelet antigen (MAIPA) were detected in at least one patient in each group, with anti-GP IIb being the most prevalent, followed by anti-GPIIIa. The WHO bleeding assessment scoring showed that most of the patients were no bleeding or only mild hemorrhage.

Responses

The primary endpoint and second endpoints are summarized in Table 2. The primary endpoint, defined as a platelet count ≥50 $\times 10^9$/L at week 8, was achieved by 40% of patients in the 100 mg group, while none in the other groups. This endpoint was less satisfactory, and can be attributed to the slower onset of action of

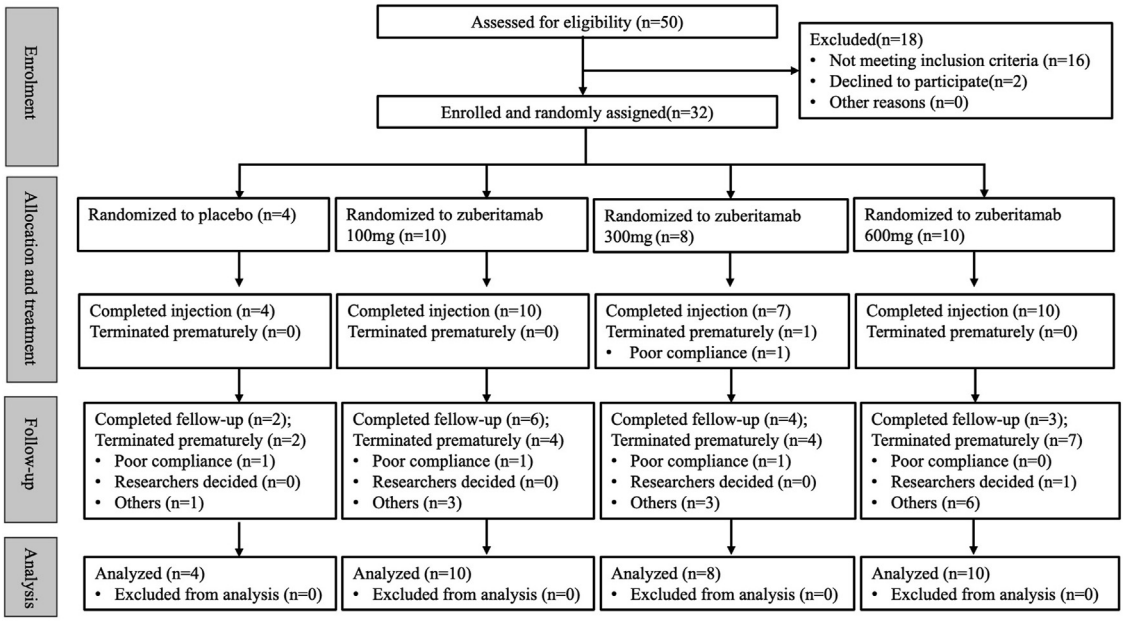

Fig. 1: Study profile and populations analyzed.

Characteristic	Placebo (n = 4)	Zuberitamab 100 mg (n = 10)	Zuberitamab 300 mg (n = 8)	Zuberitamab 600 mg (n = 10)	Total (n = 32)
Age, years (median, IQR)	38 (29–52)	53 (28–64)	53 (29–60)	34 (26–47)	45.0 (28–59)
Females, n (%)	3 (75)	8 (80)	5 (62.5)	6 (60)	22 (69)
Weight, kg (median, IQR)	61 (59–68)	63 (60–67)	61 (56–73)	64 (55–66)	62 (57–67)
ITP phase (n, %)					
Newly diagnosed	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Persistent	0 (0)	2 (20)	2 (25)	2 (20)	6 (19)
Chronic	4 (100)	8 (80)	6 (75)	8 (80)	26 (81)
Baseline PLT ($\times 10^9$/L, median, IQR)	15 (8–25)	15 (14–23)	9 (5–25)	11 (7–21)	12 (5–25)
Comorbidity (n, %)	4 (100)	9 (90)	8 (100)	10 (100)	31 (97)
Metabolic diseases	2 (50)	5 (50)	3 (38)	7 (70)	17 (53)
Hepatobiliary diseases	2 (50)	4 (40)	4 (50)	5 (50)	15 (47)
Cardiac organ diseases	1 (25)	2 (20)	0 (0)	3 (30)	6 (19)
Infectious diseases	1 (25)	5 (50)	4 (50)	3 (30)	13 (41)
Renal diseases	2 (50)	1 (10)	2 (25)	2 (20)	7 (22)
Endocrine system diseases	0 (0)	1 (10)	1 (13)	1 (10)	3 (9)
Gastrointestinal diseases	3 (75)	2 (20)	0 (0)	0 (0)	5 (16)
Previous therapy (n, %)					
Steroids	4 (100)	10 (100)	6 (75)	8 (80)	28 (88)
IVIG	2 (20)	3 (30)	1 (13)	2 (20)	8 (25)
rhTPO	2 (50)	7 (70)	3 (38)	8 (80)	20 (63)
Cyclosporin	0 (0)	1 (10)	2 (25)	2 (20)	5 (16)
Danazol	2 (50)	0 (0)	0 (0)	3 (30)	5 (16)
Azathioprine	0 (0)	1 (10)	1 (13)	0 (0)	2 (6)
Herbs	3 (75)	2 (20)	3 (38)	4 (40)	12 (38)
Number of previous treatments (n, %)					
1–3	2 (50)	7 (70)	4 (50)	5 (50)	18 (56)
≥4	2 (25)	3 (30)	4 (50)	5 (50)	14 (44)
Platelet antibodies (n, %)	1 (25)	2 (20)	5 (63)	2 (20)	10 (31)
Anti-GP I b (+)	0 (0)	1 (10)	0 (0)	0 (0)	1 (3)
Anti-GP IX (+)	0 (0)	0 (0)	1 (13)	2 (20)	3 (9)
Anti-GP II B (+)	1 (25)	1 (10)	3 (38)	0 (0)	5 (16)
Anti-GP III a (+)	1 (25)	0 (0)	2 (25)	1 (10)	4 (13)
Anti-GMP 140 (+)	0 (0)	1 (10)	1 (12.5)	0 (0)	2 (6)
TPO (pg/mL, median, IQR)	234 (122–589)	88 (51–126)	122 (50–163)	97 (66–185)	113 (57–162)
WHO bleeding score (n, %)					
0	2 (50)	7 (70)	4 (50)	5 (50)	18 (56)
1	2 (50)	2 (20)	4 (50)	5 (50)	13 (41)
2	0 (0)	1 (10)	0 (0)	0 (0)	1 (3)
3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

PLT, platelet; IQR, interquartile range; TPO, thrombopoietin; WHO, the world health organization.

Table 1: **Patient demographic and baseline characteristics.**

CD20 monoclonal antibodies, and the 8-week time frame may not be an appropriate evaluation point. Overall, a lower dosage of 100 mg zuberitamab appears to yield better efficacy, exhibit significant advantages in early response (within 8 weeks) and duration. Platelet monitoring at various time points (Fig. 2A) reveals that patients in the treatment groups generally maintain lower platelet levels within the initial 8 weeks post-administration. Notably, the 100 mg group exhibits a mild increase starting at week 5, which is sustained and remains at a stable level after week 14. Furthermore, monitoring response rates at each time point for all groups (Fig. 2B, response defined as PLT $\geq 50 \times 10^9$/L) supports similar conclusions. The effectiveness in these patients begins to stabilize at 16 weeks, fluctuating between 25% and 80%, with notable improvement and stability, especially at 22 and 24 weeks.

The duration of response was 7 (0–16) weeks, 0.5 (0–4) weeks, 0.5 (0–5) weeks, respectively. It is evident

	Placebo (n = 4)	Zuberitamab 100 mg (n = 10)	Zuberitamab 300 mg (n = 8)	Zuberitamab 600 mg (n = 10)	Zuberitamab total (n = 28)
Primary endpoint: the proportion of patients achieving PLT ≥50×10^9/L at week 8					
Week 8, n (%)	0 (0)	4 (40)	0 (0)	0 (0)	4 (14)
Second endpoint: the proportion of patients achieving PLT ≥50×10^9/L at least once within week 12/24					
Week 12, n (%)	2 (50)	7 (70)	3 (38)	5 (50)	15 (54)
Week 24, n (%)	2 (50)	7 (70)	4 (50)	5 (50)	16 (57)
Second endpoint: the proportion of patients achieving PLT ≥100×10^9/L at least once within week 12/24					
Week 12, n (%)	0 (0)	6 (60)	1 (13)	3 (30)	10 (36)
Week 24, n (%)	0 (0)	7 (70)	1 (13)	4 (40)	12 (43)
Second endpoint: PLT increased twice more than baseline as well as ≥30×10^9/L at least once during the treatment					
Week 12, n (%)	1 (25)	8 (80)	4 (50)	7 (70)	19 (68)
Week 24, n (%)	1 (25)	8 (80)	5 (63)	7 (70)	20 (71)
Second endpoint: the proportion of patients achieving the therapy target within week 12/24 (Concomitant treatment reduction, bleeding score reduced)					
Week 12, n (%)	1 (25)	4 (40)	3 (38)	4 (40)	11 (39)
Week 24, n (%)	1 (25)	5 (50)	4 (50)	5 (50)	14 (50)
Second endpoint: the proportion of patients need the rescue treatment at week 12/24					
Week 12, n (%)	0 (0)	2 (20)	0 (0)	2 (20)	4 (14)
Week 24, n (%)	0 (0)	2 (20)	0 (0)	2 (20)	4 (14)
Second endpoint					
Duration, week, (median, IQR)	1 (0–5)	7 (0–16)	0.5 (0–4)	0.5 (0–5)	3 (0–9)

PLT, platelets.

Table 2: **Primary endpoint and second endpoints.**

that although the high-dose group exhibits a faster onset of action, sustaining efficacy proves challenging. Conversely, the low-dose group, while demonstrating a relatively slower onset, maintains a favorable and prolonged therapeutic effect. Within 12 weeks, the proportions of patients in each treatment group achieving at least one instance of platelet count ≥50 × 10^9/L or ≥100 × 10^9/L, or an increase twice more than baseline as well as ≥30 × 10^9/L were (70%, 38%, 50%), (60%, 13%, 30%), and (80%, 50%, 70%) in zuberitamab 100/300/600 mg group, respectively. By week 24, the proportions of patients achieving these secondary endpoints remained relatively stable or showed a mild increase of around 10%. Furthermore, the proportion of patients in each group reaching the treatment target within week 24 was 50% in all three groups.

Throughout the study, bleeding events were reported in one patient (10%) in the 100 mg group, six patients (75%) in the 300 mg group, five patients (50%) in the 600 mg group, and two patients (50%) in the placebo group. Most of these events were graded as 1–2, with only one patient in the placebo group experiencing a grade 4 fatal cerebral hemorrhage. Notably, the bleeding situation improved with a dosage of 100 mg, reducing the number of affected individuals from three to one compared to the baseline state.

Safety and tolerability

During the treatment phase, all patient groups experienced one or more adverse events (AEs). Table 3 summarizes the incidence and severity of AEs and adverse reactions during the treatment, while Table 4 provides details on specific AE events across groups. The majority of AEs were of grade 1–2 severity (mild to moderate) and resolved without the need for medical intervention. The occurrence rates and severity of AEs were comparable among the three treatment groups.

The most common AEs included infections (n = 14, 50%), fever (n = 14, 50%), various metabolic and nutritional disorders (n = 11, 39%), and gastrointestinal injuries (n = 11, 39%). Six patients experienced grade 3 or higher adverse reactions, including one case of anemia during the 300 mg treatment, and four cases of severe thrombocytopenia during the course of treatment. Both these AEs were deemed unrelated to the investigational drug. Additionally, one patient in the 600 mg group developed pulmonary infection, and another in the 100 mg group reported headache; these two AEs were considered drug-related.

Additionally, apart from mild hypogammaglobulinemia observed in one patient each in the higher dose groups (300 mg, 600 mg), there were no other occurrences in the treatment groups. No other grade 4 adverse reactions, deaths, or thrombotic events were reported in the treatment groups. In the placebo group, one patient succumbed to cerebral hemorrhage. In the three treatment groups, the incidence of adverse reactions was higher in the high-dose group compared to the low-dose group, with a rate of 90% observed in the 600 mg group. Infusion reactions related to the

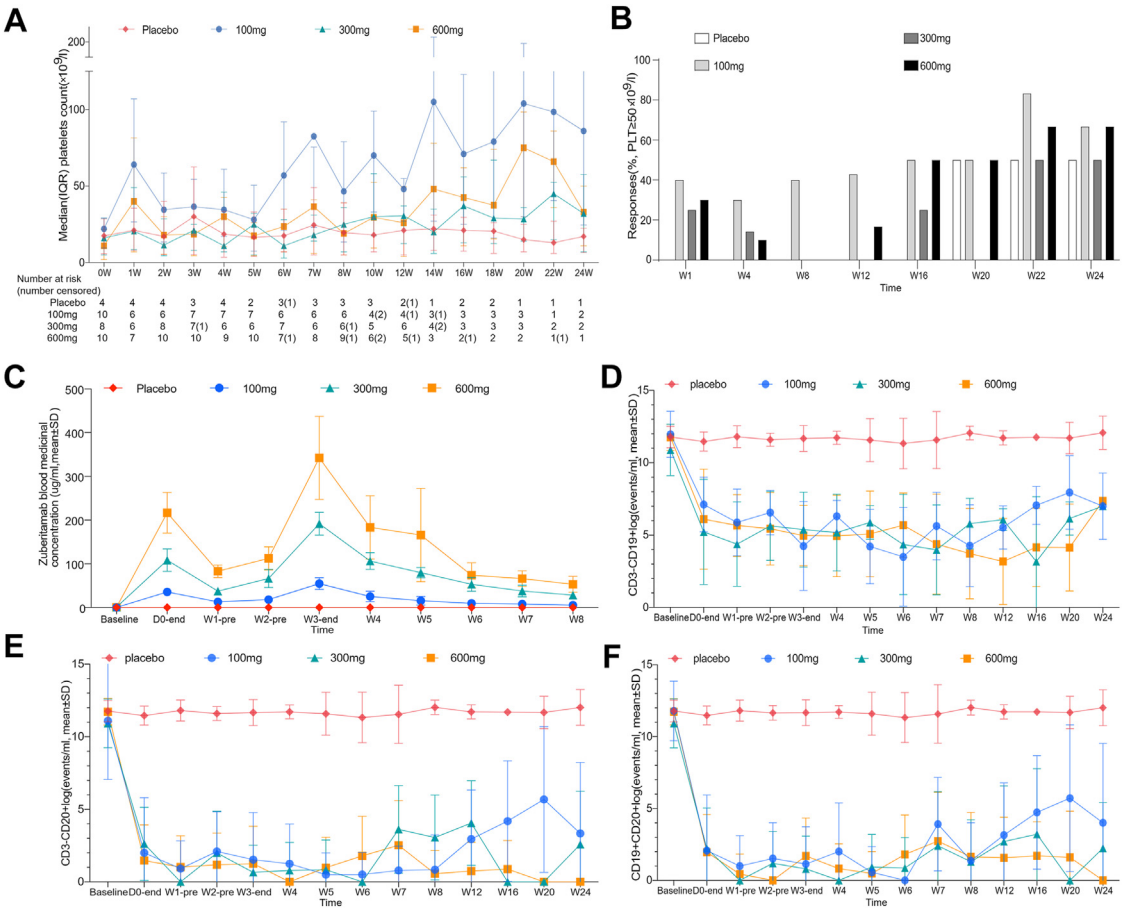

Fig. 2: Platelet counts and responses; the mean plasma concentration and immunogenicity analyses. (A) Median platelet counts at every visit; (B) response rate of PLT ≥50 × 10^9/L at every visit. (C) the mean plasma concentration–time profile of zuberitamab; (D) the comparative clearance efficacy of CD3-CD19 + B cells; (E) the comparative clearance efficacy of CD3-CD20 + B cells; (F) the comparative clearance efficacy of CD19 + CD20 + B cells. "end" means within 5 min after the drug injection, "pre" means within 2 h before the drug injection.

investigational drug accounted for the highest proportion, reaching 70% in the 600 mg group. However, adverse events of grade ≥3 were rare, occurring in only one patient each in the 100 mg and 600 mg groups, manifesting as headache and infectious pneumonia, respectively. Moreover, among the reported adverse reactions, up to 50% led to treatment suspension in the 600 mg group.

Pharmacokinetic, pharmacodynamic and immunogenicity analyses

Fig. 2C illustrates the mean concentration–time curves for zuberitamab. The plasma concentration of zuberitamab as well as pharmacokinetic parameters such as C_{max}, and C_{min} showed an increasing trend with dose 100 mg–600 mg. The dosing regimen is within the linear pharmacokinetic behavior of zuberitamab. The accumulation trend was observed in the 3 dose groups after multiple-doses (4 weekly infusion), but gradually decreased to baseline during the subsequent follow-up period (Supplementary Table S2).

In patients across three dosage cohorts treated with zuberitamab, CD19 + B cells and CD20 + B lymphocytes rapidly declined to 0% within one week and consistently maintained reduced B lymphocyte levels throughout the entire treatment phase. However, the low-dose cohort (100 mg) exhibited a partial rebound in CD20 + B cells proportions after week 16, subsequently regressing to a sustained low-level state observed at the initiation of treatment. The placebo group displayed fluctuations within the initial range of lymphocytes throughout the study period (Fig. 2D–F).

All 28 patients with negative antidrug antibody (ADA) status at baseline (the placebo group without immunogenicity detection), and 3 patients (2 in 100 mg and 1 in 600 mg group) tested positive ADA for anti-zuberitamab antibodies at one or more time points in this trial during the whole treatment period. No patients developed

	Placebo (n = 4)		Zuberitamab 100 mg (n = 10)		Zuberitamab 300 mg (n = 8)		Zuberitamab 600 mg (n = 10)	
	times	n, %	times	n, %	times	n, %	times	n, %
Adverse event	22	4 (100)	95	10 (100)	60	8 (100)	82	10 (100)
Serious adverse event	1	1 (25)	3	2 (20)	3	2 (25)	4	3 (30)
≥ Grade 3 adverse event	2	2 (50)	3	3 (30)	1	1 (13)	3	2 (20)
Adverse events resulting in dose reduction	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Adverse events resulting in increased dose	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Adverse events that lead to delayed dosing	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Adverse events leading to suspension of dosing	0	0 (0)	5	2 (20)	3	1 (13)	11	5 (50)
Adverse events leading to drug discontinuation	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (10)
Adverse events leading to patient withdrawal	0	0 (0)	1	1 (10)	0	0 (0)	0	0 (0)
Adverse events leading to death	1	1 (25)	0	0 (0)	0	0 (0)	0	0 (0)
Adverse reaction	0	0 (0)	26	6 (60)	14	5 (63)	45	9 (90)
Serious adverse reaction associated with investigational drugs	0	0 (0)	1	1 (10)	1	1 (13)	1	1 (10)
Infusion reactions associated with the investigational drug	0	0 (0)	16	4 (40)	8	4 (50)	20	7 (70)
≥ grade 3 adverse reactions	0	0 (0)	1	1 (10)	0	0 (0)	1	1 (10)
Adverse reactions resulting in dose reduction	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Adverse reactions resulting in increased dose	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Adverse reactions that lead to delayed dosing	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Adverse reactions leading to suspension of dosing	0	0 (0)	5	2 (20)	3	1 (13)	11	5 (50)
Adverse reactions leading to drug discontinuation	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Adverse reactions leading to patient withdrawal	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Adverse reactions leading to death	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)

Table 3: **The occurrence of adverse events and adverse reactions.**

neutralizing activity for anti-zuberitamab antibodies during the whole treatment period (Supplementary Table S3).

Factors influencing response rates

Due to the limited number of cases, we restricted our analysis to preliminary observations of potential factors affecting zuberitamab treatment, as reported in the previous studies.[15–18] Overall, female patients exhibited superior responses compared to male patients. In the 100 mg/m^2 group, the response rate for females reached 50%, while males failed to achieve a response. Patients with a disease duration of less than one year demonstrated a higher response rate (100%) than those with a duration exceeding one year (25%). Additionally, MAIPA-positive patients exhibited a significantly higher response rate than those negative patients. However, due to the limited number of antibody-positive individuals, these data serve as reference and cannot undergo statistical analysis for differences (Supplementary Table S4).

Discussion

Zuberitamab, an innovative anti-CD20 monoclonal antibody, was initially developed in China and introduced for the treatment of diffuse large B lymphoma. It exhibits a more advantageous profile in B cell clearance. This prospective, dose-escalation, phase II study in ITP demonstrated that zuberitamab was well tolerated, with most AEs of grade 1 or 2, there was no severe infections and hypogammaglobulinemia occurred. Anticipated therapeutic dose of zuberitamab was 100 mg, leading to a response rate (PLT ≥50 × 10^9/L) of 40%–80% within week 24 and have an early response. And the 100 mg of zuberitamab was enough to clear B cells rapidly and completely. We also observed that women, disease duration <12 months, and MAIPA-positive patients may have higher response rates, but this was not rigorous due to the limited patients. This study preliminarily confirmed that zuberitamab is safe and effective in treating Chinese adults ITP patients.

The primary objectives of current ITP treatments are to reduce the risk of bleeding, maintain platelet counts at safe levels, and minimize mortality. While corticosteroids have been recommended for years as the first-line treatment for ITP, approximately 80% of adult patients with ITP failed to respond or become corticosteroid-dependent, necessitating second-line treatment.[3,4] As second-line treatment, RTX offers a finite number of administrations that result in a long treatment-free response, patients do not have to take any ITP medication, and can evade frequent hospitalizations.[6,7] Based on a review of rituximab treatment in ITP patients, it was observed that both adults and children exhibited initial overall response rates of 40%–60%, with similar 5-year estimates of persistent response 21% and 26%, respectively.[19] Concurrently, a meta-analysis reported that rituximab was associated with an overall response rate

Adverse event	Placebo (n = 4)				Zuberitamab 100 mg (n = 10)				Zuberitamab 300 mg (n = 8)				Zuberitamab 600 mg (n = 10)			
	Times	Number of cases (%)	CTCAE classification		Times	Number of cases (%)	CTCAE classification		Times	Number of cases (%)	CTCAE classification		Times	Number of cases (%)	CTCAE classification	
			<3	≥3			<3	≥3			<3	≥3			<3	≥3
Fever	0	0 (0)	0	0	8	4 (40)	4	0	5	4 (50)	4	0	6	6 (60)	6	0
Metabolic disorders	6	2 (50)	2	0	8	3 (30)	3	0	9	2 (25)	2	0	19	6 (60)	6	0
Tissue injuries	1	1 (25)	1	0	2	1 (10)	1	0	3	3 (38)	3	0	4	4 (40)	4	0
Decreased platelet count	0	0 (0)	0	0	2	2 (20)	0	2	0	0 (0)	0	0	2	2 (20)	0	2
Elevated γ-glutamyl transferase	0	0 (0)	0	0	0	0 (0)	0	0	0	0 (0)	0	0	2	1 (10)	1	0
Elevated alanine aminotransferase	0	0 (0)	0	0	0	0 (0)	0	0	1	1 (13)	1	0	1	1 (10)	1	0
Lymphocyte count decreased	0	0 (0)	0	0	3	1 (10)	1	0	0	0 (0)	0	0	0	0 (0)	0	0
Immunoglobulin A decreased	0	0 (0)	0	0	0	0 (0)	0	0	1	1 (13)	1	0	0	0 (0)	0	0
Impairment of gastrointestinal	1	1 (25)	1	0	15	5 (50)	5	0	2	2 (25)	2	0	7	4 (40)	4	0
Impaired cardiac function	2	1 (25)	1	0	0	0 (0)	0	0	1	1 (13)	1	0	4	3 (30)	3	0
Infection	7	3 (75)	3	0	11	6 (60)	6	0	7	5 (63)	5	0	5	3 (30)	2	1
Damage to the hepatobiliary system	1	1 (25)	0	1	2	2 (20)	2	0	0	0 (0)	0	0	3	2 (20)	2	0
Hypotension	0	0 (0)	0	0	5	2 (20)	2	0	1	1 (13)	1	0	2	2 (20)	2	0
Hypogammaglobulinemia	0	0 (0)	0	0	0	0 (0)	0	0	1	1 (13)	1	0	1	1 (10)	1	0
Giddy	0	0 (0)	0	0	1	1 (10)	1	0	2	1 (13)	1	0	1	1 (10)	1	0
Headache	1	1 (25)	1	0	9	4 (40)	3	1	0	0 (0)	0	0	0	0 (0)	0	0
Intracranial hemorrhage	1	1 (25)	0	1	0	0 (0)	0	0	0	0 (0)	0	0	0	0 (0)	0	0
Respiratory system damage	0	0 (0)	0	0	2	2 (20)	2	0	2	1 (13)	1	0	1	1 (10)	1	0
Ocular dysfunction	0	0 (0)	0	0	4	2 (20)	2	0	3	3 (38)	3	0	2	1 (10)	1	0
Damage to kidney system	1	1 (25)	1	0	0	0 (0)	0	0	1	1 (13)	1	0	1	1 (10)	1	0
Anaemia	0	0 (0)	0	0	1	1 (10)	1	0	2	1 (13)	0	1	2	1 (10)	1	0
Eosinophilia	0	0 (0)	0	0	1	1 (10)	1	0	0	0 (0)	0	0	0	0 (0)	0	0
Iron deficiency anemia	0	0 (0)	0	0	0	0 (0)	0	0	2	1 (13)	1	0	0	0 (0)	0	0
Stun	1	1 (25)	1	0	0	0 (0)	0	0	0	0 (0)	0	0	0	0 (0)	0	0

CTCAE, common terminology criteria for adverse events.

Table 4: **The occurrence of adverse events of varying severity in different systems during patient treatment.**

(ORR) of 57% and a complete response rate (CRR) of 41%, the mean time to response was 6.34 weeks, and the median duration of response was 12 months.[20] While the primary endpoint was less satisfactory in our study, particularly in the mid-dose and high-dose groups, this can be attributed to the slower onset of action of CD20 monoclonal antibodies, and the 8-week time frame may not be an appropriate evaluation point. The effectiveness in these patients begins to stabilize at 16 weeks, fluctuating between 25% and 80%, with notable improvement and stability, especially at 22 and 24 weeks.

Furthermore, this study explored the anticipated therapeutic dose. The results indicated that zibetuzumab did not elevate platelet count in a dose-dependent exposure-efficacy manner, with the recommended dose being 100 mg.[3,9] Further investigation through large randomized clinical trials needs to be undertaken. Despite significant depletion of peripheral blood B cells observed in patients across the three groups, we cannot comprehensively elucidate why the therapeutic effect of high-dose zibetuzumab is lower than that of the low-dose, particularly before 12 weeks. It is possible that gender, disease duration, and platelet autoantibodies—factors that may influence efficacy—were not evenly distributed among the groups. The response rate in the placebo group reached 50% at 12 weeks, potentially attributed to the inclusion of only four cases in the placebo group.

Safety is a general concern in studies evaluating immunosuppressive drugs in chronic disease. Zuberitamab was well tolerated, most of the adverse events were mild to moderate. No deaths were reported, and there were no instances of severe adverse events, particularly no severe infections. A slight decrease in immunoglobulins was observed in the 600 mg group, but gradually recovered at week 20 (Supplementary Figure S1). This finding partially similar to some initial studies, which have described prolonged hypogammaglobulinemia and an increased risk of certain infections in a subset of patients receiving rituximab.[21–23] An elevated risk of infections following rituximab therapy is generally uncommon and is more frequently

observed in severely immunocompromised patients.[24] However, a meta-analysis encompassing five trials and 463 ITP patients treated with rituximab did not reveal an increased risk of infection.[25] Khellaf et al. concluded that the risk of infections was deemed acceptable, with a cumulative incidence of 2.3 infections per 100 patient-years at a median follow-up of 24 months.[8] The most severe infections were observed in adults older than 70 years of age with significant comorbidities. Consistent with previous studies, infusion reactions were common.[8] This phenomenon is attributed to immune activation against the chimeric mouse-human drug, leading to the formation and deposition of immune complexes and subsequent activation of the complement cascade.[26]

The plasma exposure of zuberitamab in ITP patients increased following the initial administration, and reached its peak after the final dose, consistent with previous observation in diffuse large B lymphoma patients (unpublished data). The depletion of circulating B cells after zuberitamab administration is rapid, occurring within 1 week, and profound, with B-cell counts remaining low in the peripheral blood for at least 24 weeks, providing a more advantageous profile compared to rituximab.[27] Our study demonstrated that a dose of 100 mg zuberitamab was sufficient to clear B cells, and higher doses of the drug do not result in higher response rates. A previous study investigated 18 spleens removed from ITP patients, whether treated or not with RTX, and observed that, although B cells were implicated in ITP pathogenesis, RTX-induced total B-cell depletion was not necessarily correlated with its therapeutic effects.[28] This suggested that additional immune modulators, such as T cells and Treg cells, may play a role in the efficacy of those drugs.

To explore the reasons for the unsatisfactory efficacy in the 300 mg and 600 mg dosage groups, we conducted a statistical analysis of the baseline peripheral blood B-cell counts of the subjects. The results suggested that compared to the 100 mg group, both the 300 mg and 600 mg groups had lower peripheral blood B-cell counts. We hypothesized that the higher B cell levels in the 100 mg dosage group play a predominant role in its pathogenic mechanism, leading to improved efficacy outcomes in patients from this group. And our previous data indicates that our drug has better CD20 affinity compared to RTX. Therefore, we believe that a dosage of 100 mg is sufficient for the treatment of ITP. Higher doses may lead to prolonged accumulation of CD20 antibodies in the body, potentially causing sustained activation of the complement system,[29,30] increased secretion of inflammatory factors such as IFN-γ, thereby elevating the Th1/Treg ratio and promoting the activation of cytotoxic T cells,[31] leading to increased platelet destruction and ineffective treatment. Furthermore, we found that there was a higher proportion of patients in the 300 mg and 600 mg groups who had received ≥3 prior treatments, which may have contributed to these patients being more resistant to the drug. Previous studies have found that young age, female gender, short duration of disease, antiplatelet autoantibodies, the achievement of complete response, and few previous treatments may be associated with the sustained response of rituximab.[16–18] We also observed that women, disease duration <12 months, and MAIPA-positive patients had higher response rates, but this was not rigorous due to the limited number of cases. Larger clinical trials with more patients and longer follow-up time are needed to verify this conclusion. The role of antiplatelet autoantibodies (APA) as predictive factors for response is highly controversial. A previous study showed that neither the presence of autoantibodies at baseline nor the disappearance of autoantibodies after treatment was associated with the response to rituximab, but the persistence of platelet autoantibodies can serve as a marker of disease severity.[32] While Porcelijn et al. proposed that, response to rituximab appeared to be associated with a decline in platelet-bound antibody, implicating that lack of detectable platelet autoantibodies was correlated with non-responsiveness to rituximab.[33] In a recently published article reported that ANA positive ITP cases have a statistically significant better ORR than ANA negative ITP patients.[15] These confusing results indicated that the biomarkers of response to anti-CD-20 monoclonal in ITP need to be further investigated.

It is noteworthy that the economic aspect of treatment remains a crucial point. Traditional dosing of rituximab would entail high costs, with each treatment cycle costing approximately 4361$.[10] This high cost limits the use of this drug for patients without strong economic support.[11] The rituximab same target drug reduced the cost, making it an economically viable option for the treatment of relapsed and refractory ITP in resource-limited settings.[14] According to their approval procedure, those drugs have been previously evaluated head-to-head against the reference product in large randomized controlled trials for the treatment of follicular lymphoma and rheumatoid arthritis, with reassuring results, but not for ITP indications.[12,13] This prospective study is the first to investigate the efficacy and safety of zuberitamab in the Chinese ITP population, providing valuable clinical data for the subsequent inclusion of ITP indications and incorporation into Chinese medical insurance. It offers convenience in reducing treatment costs and provides pathways for the use of CD20 monoclonal antibodies for Chinese ITP patients. It is estimated that Zuberitamab requires approximately 781$ per treatment cycle, significantly less than rituximab.

This study had several limitations. Firstly, the number of patients was small. Further large clinical trials are required to verify the efficacy and safety of zuberitamab in ITP. Secondly, the follow-up period of this study was

only 24 weeks, lack of long-term maintenance efficacy observational data. Thirdly, research indicates that the efficacy of CD20 monoclonal antibodies is not solely attributed to their impact on B cells, but also involves modulation of T cell immunity. Regrettably, our study did not assess the T-cell immune status before and after treatment. In addition, many patients had received multiple therapy. However, given the chronicity of ITP in adult patients, these patients represent those in need of treatment in current clinical practice.

In conclusion, this study demonstrated that zuberitamab seem an effective and safe alternative to consider in the current therapeutic armamentarium. This is reflected in three aspects: mild to moderate adverse events, rapid and complete clearance of B cells, and an efficacy rate similar to rituximab. The administration of zuberitamab at a dose of 100 mgonce weekly was chosen as the anticipated therapeutic regimen for chronic ITP patients and recommended to support further phase III trials. The utilization of zuberitamab for ITP treatment holds promise for reducing the treatment cost burden on the challenged healthcare system and provides convenient access to the medications for Chinese patients.

Contributors

HM and YH conceptualised and designed the study. HM, YH, MX and JS wrote this article. HM, YH, MX, JS, SQ, JG, YG, RH, SW, ZeZ, GY, MH, LiL, S Lou, YS, QL and HZ collected, analysed and interpreted the data, and critically reviewed and approved the final version of this report. All authors reviewed and commented on the manuscript before publication.HM and MX accessed and verified all the data in the study. HM had full access to all the data in the study. HM and YH had final responsibility for the decision to submit for publication.

Data sharing statement

The study protocol and individual deidentified participant data that underlie the results reported in this Article, will be available to researchers who provide a reasonable method proposal. For meta-analysis purposes, individual participant data will become available between 9 months and 36 months after Article publication, and proposals should be directed to hmei@hust.edu.cn. To gain access, data requestors will need to sign a data access agreement.

Declaration of interests

All co-authors received funding from *Zhejiang Bioray Biopharmaceutical Co. Ltd.*. The company provided the investigate drugs and financial support throughout the clinical trial, such as patient compensation and the examination costs (MAIPA, B-cell subpopulation determination et al.). The other work in this clinical trial, including study design, data collection, data analysis, data interpretation and writing of the report et al. were jointly conducted by authors Min Xu, Jinhui Shu, Heng Mei, Yu Hu et al. The company has no objection to the contributions described in the manuscript, and there are no conflicts of interest between the company and all co-authors.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101096.

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