การศึกษาประสิทธิภาพของยาขนานที่สองในการรักษาผู้ป่วยโรคเกล็ดเลือดต่ำจากภูมิคุ้มกัน

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บทคัดย่อ

การทบทวนเอกสารอย่างป็นระบบชิงปริมาณหลายการศึกษาแสดงให้เห็นถึงการรักษาที่สองในผู้ป่วย ITP พบว่าเอลทรอมโบแพกแท็บเล็ต (eltrombopag) ริทูซิแมบ(rituxinab) การตัดม้าม(splenectomy)ผู้ป่วยส่วนมากมีผลตอบสนองที่เพิ่มจำนวนเกล็ตเลือดได้มากกว่า 100,000/L และลตภาวะเลือดออกผิดปกตินอกจากนี้การศึกษาในยาคอลชิซีน (colchicine) ยาดานาซอล (danazol) ยาแดพโซน (dapsone) และ ยาเอซาไธโอพรีน (azathioprine)มีการศึกษาน้อย ผลการตอบสนองต่อการรักษาไม่แน่ชัด จึงได้ทำการศึกษาการรักษาที่สองของผู้ป่วย IP ในบริบทของ รพ.สระบุรี การศึกษานี้ศึกษาผลการตอบสนองและระดับเกล็ดเลือดหลังได้รับของการรักษาขนานที่สองในผู้ป่วย TP ที่ไม่ตอบสนองต่อยารักษา TP ขนานแรก รูปแบบการศึกษาเป็นการวิจัยแบบย้อนหลัง ศึกษาการตอบสนอง ระดับเกล็ดเลือด และผลข้างเคียงจากการรักษา ได้แก่ การแข็งตัวของเลือดผิดปกติ ภาวะเลือดออก ตับอักเสบ หลังได้รับของการรักษาขนานที่สอง 6 เดือนผู้ป่วย idiopathic ITP มีอายุตั้งแต่ 15 ปีขึ้นไป ที่ไม่ตอบสนองต่อยารักษา TP ขนานแรกจากกรรักษาด้วยยา eltrombopag ย1 rituximab การตัดม้าม ย1 colchicineยาdanazolยาdapsone หรือการใช้ยาควบคู่มกราคม 2550 - ธันวาคม 2564 ในโรงพยาบาลสระบุรี ผู้เข้าร่วมวิจัยทั้งหมด 51 คน เป็นเพศหญิงร้อยละ 76.4 ยา eltrombopag ตอบสนองcomplete response (CR) ร้อยละ 100 การรักษาการตัดม้าม ยาazathioprine ยา colchicines และ ยาdapsone ตอบสนองโดยรวมมากกว่าร้อยละ 80 สำหรับการรักษาจากcochicine ร่วมกับ dapsone ตอบสนองร้อยละ 60 CR ร้อยละ 62.5 azathioprine ร่วมกับ dapsone และ azathioprine ร่วมกับ colchicines ตอบสนองแบบ PR และ danazol ไม่มีการตอบสนอง ผลข้างเคียงจากกรรักษาไม่พบตับอักเสบรุนแรง ภาวะเลือดออกรุนแรงพบได้น้อย ภาวะการแข็งตัวของเลือดผิดปกติพบน้อย ปัจจัยกี่ยวกับผู้ป่วยที่รับการรักษาและการรักษาด้วยการรักษาขนานที่สองกับการตอบสนองการักษาไม่มีนัยสำคัญทางสถิติ การรักษาด้วย e(trom bopag และการตัดม้ามได้ผลการตอบสนองและใช้รักษาที่สองได้ดี นอกจากนี้ยา colchicine dapsone azathioprine หรือการนำยาสองชนิดดังที่กล่าวข้างต้นมรักษาร่วมกันสามารถนำมาใช้เป็นทางเลือกสำหรับ second line treatment of idiopathic ITPแต่ผลของการรักษาด้อยกว่าการรักษาด้วย eltrombopag และการตัดม้าม

คำสำคัญ: idiopathic ITP, eltrombopag, splenectomy,colchicine, dapsone, azathioprine

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The Efficacy of Second Line Therapies in Immune Thrombocytopenia Purpura patient

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Abstract

A systematic meta-analysis reported that eltrombopag, rituximab, and splenectomy were effective treatments for elevating platelet counts to more than 100,000/L and decreasing abnormal bleeding in ITP patients. However, the beneficial effects of second-line treatment for ITP, including colchicine, dapsone, azathioprine, and danazol, are unclear due to limited research. This study assessed the efficacy of second-line ITP treatment for patients in Saraburi hospitals in Thailand. This study aims to evaluate efficacy and platelet count after 6 months of second-line treatment in patients with idiopathic ITP. The authors conducted a retrospective study to assess the efficacy of 6-month treatment with eltrombopag, rituximab, splenectomy, colchicine, dapsone, azathioprine, danazol, combination treatment of colchicine with azathioprine or dapsone, and azathioprine with dapsone on treatment response, including platelet count. Other adverse events, including abnormal bleeding, thrombosis, hepatitis will also be analyzed the analysis includes patients with idiopathic ITP patients aged above 15 years old who were treated at Hematology Clinic in Saraburi Hospital (Thailand) between January 2007 and December 2022. 51 Idiopathic ITP patients were 76.4% female. Patients treated with eltrombopagwere all completely responsive, while patients treated with splenectomy, azathioprine, colchicine, and dapsone have an overall response rate of more than 80%. The combination of colchicine and dapsone produced an overall response of 60% with a complete response of 20%. Other combinations of azathioprine with dapsone or colchicine provided a partial response. Patients who were treated with danazol had no response to such treatment. In this study, the adverse events from second-line treatment such as severe bleeding, thrombosis, and severe hepatitis event were low. All patients' characteristic factors and second-line ITP treatments associated with treatment response did not meet any statistical significance. Eltrombopag and splenectomy provide a good clinical response rate and are commonly used for second-line ITP treatments. Despite the fact that colchicine, dapsone, azathioprine, and combination therapy have been used for second-line ITP treatment in clinical practice, their efficacy for ITP treatment was reported to be inferior to that of eltrombopag and splenectomy.

Key words: idiopathic ITP, eltrombopag, splenectomy, colchicine, dapsone, azathioprine

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Introduction

Immune thrombocytopenic purpura (ITP) is a disease that occurs in 2 to 5 out of every 100,000 people per year, according to statistics in the United States in 2014. However, this disease is important because it has low platelet counts that may cause organ bleeding. Thus, idiopathic ITP patients are more likely to die from abnormal bleeding. The primary treatment is the steroid prescription of prednisolone or dexamethasone, but steroid treatment has a lot of side effects, and some patients don't respond to steroid therapy, so they are given second-line treatment of ITP to reduce the dose of steroid and for better response. [1,2,3,4]Current treatmentsin clinical practice include colchicine, danazol, dapsone, eltrombopag, rituximab, splenectomy, azathioprine, or combination therapy. Previous studies found that eltrombopag increases platelet count levels. [2,5]Eltrombopag is recommended treatment in Thai guidelines for treatment of ITP in 2022. [2] The treatment of eltrombopag could increase levels of platelet count and reduce abnormal bleeding. However, the Thai health care policy, such as universal coverage, and the social security scheme didn't allow for reimbursement of such treatment. Alternative drugs such as rituximab [6], splenectomy [2,7], azathioprine [8], colchicine [9], and dapsone [10] were employed to treat primary ITP patients, although their efficacies of the drugs were uncertain.

This research aims to study the efficacy of treating primary ITP with colchicine, danazol, dapsone, azathioprine, eltrombopag, and rituximab, and combinations of these therapies as second-line management.

Patients and Methods

Study design

This is a retrospective cohort study to evaluate the response of available second-line treatments for treating ITP at Saraburi Hospital.

Method and Study population

Idiopathic thrombocytopenic purpura (ITP) patients who were treated and followed up at the Hematology clinic, Saraburi Hospital, between 1st January 2007 and 31st December 2022 were recruited into the study. The patients were classified into three groups: relapsed ITP, refractory ITP, and steroid-dependent ITP. Information regarding patients' characteristics and treatments was recorded based on electronic medical records. Second-line treatments for ITP included eltrombopag, rituximab, splenectomy, azathioprine, dapsone, colchicine, danazol, and combination therapies

Ethic

This study has been conducted under good clinical practice and approved by Saraburi hospital ethical committee for clinical research number SRBR64-044.

Inclusion criteria

1. Primary ITP patients aged 15 years and older who were diagnosed with 3 types of ITP including relapsed ITP, refractory ITP, steroid-dependent ITP
2. Patients treated with second-line therapy, including colchicine, danazol, dapsone, eltrombopag, rituximab, and splenectomy, had been followed up for treatment at least 6 months after receiving the second-line therapy.

Exclusion criteria

1. Patients with other autoimmune diseases such as systemic lupus erythematosus (SLE), ITP from drugs, HIV, hepatitis C (HCV), and cancer.
2. Treatment follow-up periodof less than 6 months.

Outcome measurements

Primary outcome: response rate and platelet count levels after 6 months of second-line treatment in patients with idiopathic ITP.

Secondary outcomes:

1. Treatment complications include abnormal bleeding, constipation, and hepatitis.
2. Survival rate of each second-line treatment of ITP.
3. Response duration period after second-line treatment of ITP.

Definition

1. Immune thrombocytopenia (ITP) is a disease with low serum platelet count levels due to its destruction by immune mechanisms.(11)
2. Primary or idiopathic ITPis an ITP disease that occurs without a known cause. (11)
3. ITP consists of three types(11)

3.1. Relapsed ITP: the recurrence of ITP after at least 3 months of sustained remission without treatment.

3.2. Refractory ITP: ITP that does not respond to at least one month of treatment with prednisolone 1 mg/kg/day or an equivalent dose of another steroid.

3.3. Steroid-dependent ITP: ITP patients who need to receive a prednisolone dose of at least 20 mg/day to maintain their platelet count above 30,000/L to prevent bleeding.

4.Treatment responsibility of ITP patients

4.1. Complete response (CR) means platelet counts greater than 100,000/L and no abnormalbleeding.

4.2. Partial Response (PR) means that platelet count more than 30,000/L and increase for more than twofold when compared to pre-treatment platelet count with no abnormal bleeding.

4.3. No response (NR) means that platelet count less than 30,000/L or decrease more than two times when com

pared to pre-treatment platelet count or abnormal bleeding.

Statistical analysis

Median, and mean statistics were employed to find average values corresponding and its standard deviation. A percentage was used for analyzing patients' characteristics, such as the number of patients in each group. Chi-square tests and the ANOVA tests were used to test whether which factors influenced the response. the static P-value was less than 0.05. The analyses were conducted in IBM SPSS Statistics 26.

Results

Baseline characteristics

Fifty-one participants were recruited into the study. The population was predominantly female (76.4%). There were 3 types of primary ITP including relapse ITP (21.5%), refractory ITP (37.3%), and steroid-dependent ITP (41.2%). Participants were classified into 9 groups according to the second-line treatment received: eltrombopag(7.8%), splenectomy (13.7%), azathioprine (25.5%), colchicine (21.6%), danazol (1.9%), dapsone

(15.7%), azathioprine combined with colchicine (1.9%), colchicine combined with dapsone (9.8%), and azathioprine combined with colchicine (1.9%).The majority of the patients received steroids along with the second-line therapy. Of these patients, 50.1% used steroid less than 0.5 mg/kg/day of prednisolone or equivalent and 45.1% used steroids at a dose of more than 0.5 mg/kg/day of prednisolone or equivalents. Leaving 4.8% received second-line therapy only (without steroid), as shown in Table 1.The median platelet count prior to the second-line treatment groups were: eltrombopag 26,000/L, azathioprine 20,000/L,azathioprine plus colchicine 16,000/L, dapsone 11,000/L, colchicine 10,000/L,splenectomy 9,000/L, azathioprine plus colchicine 8,000/L, colchicine plus dapsone 8000/L and danazol 6,000/L, as shown in Table 1.

Table1: Baseline characteristic of second-line treatment primary ITP patients

	Eltrombopag	Splenectomy	Azathioprine,	Colchicine	Danazol
n	4	7	13	11	1
Age at treatment, mean ± SD.	63.25 ± 12.45	34 ± 14.15	48.69 ± 19.33	43.18 ± 15.56	40
Sex					
Female (39)	3 (75%)	7 (100%)	10 (76.9%)	7 (63.6%)	1 (100%)
Male (12)	1 (25%)	0 (0%)	3 (23.1%)	4 (36.4%)	0 (0%)
Underlying disease					
DM (11)	0 (0%)	0 (0%)	4 (30.8%)	2 (18.2%)	1 (100%)
HT (13)	1 (25%)	0 (0%)	5 (38.5%)	2 (18.2%)	0 (0%)
Other (6)	1 (25%)	0 (0%)	1 (7.7%)	1 (9.1%)	0 (0%)
None (29)	2 (50%)	7 (100%)	6 (46.2%)	8 (72.7%)	0 (0%)
Bleeding site at diagnosis					
GI bleeding (4)	0 (0%)	0 (0%)	1 (7.7%)	1 (9.1%)	0 (0%)
Intracranial hemorrhage (2)	0 (0%)	1 (14.3%)	0 (0%)	0 (0%)	0 (0%)
Hematuria or hypermenorrhea (6)	0 (0%)	2 (28.6%)	1 (7.7%)	1 (9.1%)	0 (0%)
Epistaxis needs to doing transfusion (1)	0 (0%)	0 (0%)	1 (7.7%)	0 (0%)	0 (0%)
Petechiae (28)	2 (50%)	4 (57.1%)	8 (61.5%)	6 (54.5%)	1 (100%)
Bleeding wound (2)	0 (0%)	0 (0%)	1 (7.7%)	0 (0%)	0 (0%)
No bleeding (8)	2 (50%)	0 (0%)	1 (7.7%)	3 (27.3%)	0 (0%)
Severity					
Mild bleeding without transfusion (33)	2 (50%)	4 (57.1%)	11 (84.6%)	5 (45.5%)	1 (100%)
Bleeding with transfusion (3)	0 (0%)	0 (0%)	0 (0%)	2 (18.2%)	0 (0%)
Life threatening bleeding, hypovolemic shock (7)	0 (0%)	3 (42.9%)	1 (7.7%)	1 (9.1%)	0 (0%)
No bleeding (8)	2 (50%)	0 (0%)	1 (7.7%)	3 (27.3%)	0 (0%)
Type of ITP					
Relapsed ITP (11)	2 (50%)	0 (0%)	3 (23.1%)	3 (27.3%)	0 (0%)

	Eltrombopag	Splenectomy	Azathioprine,	Colchicine	Danazol
n	4	7	13	11	1
Refractory ITP (19)	2 (50%)	2 (28.6%)	3 (23.1%)	5 (45.5%)	1 (100%)
Steroid-dependent ITP (21)	0 (0%)	5 (71.4%)	7 (53.8%)	3 (27.3%)	0 (0%)
Steroid treatment					
No steroid (2)	0 (0%)	0 (0%)	2 (15.4%)	0 (0%)	0 (0%)
< 0.5 mg/kg/day of prednisolone or another steroid dose equivalent (26)	2 (50%)	5 (71.4%)	8 (61.5%)	4 (36.4%)	0 (0%)
≥0.5 mg/kg/day of prednisolone or another steroid dose equivalent (23)	2 (50%)	2 (28.6%)	3 (23.1%)	7 (63.6%)	1 (100%)
Platelet count prior to second line treatment median (IQR)	26,000 (14,500, 32,000)	9,000 (4,000, 12,000)	20,000 (10,000, 30,000)	10,000 (7,000, 26,000)	6,000

Table1: Baseline characteristic of second-line treatment primary ITP patients (continue)

	Dapsone	Azathioprine plus dapsone	Colchicine plus dapsone	Azathioprine plus colchicine
n	8	1	5	1
Age at treatment, mean ± SD.	59.38 ± 15.86	27	48.6 ± 12.5	70
Sex				
Female (39)	6 (75%)	1 (100%)	3 (60%)	1 (100%)
Male (12)	2 (25%)	0 (0%)	2 (40%)	0 (0%)
Underlying disease				
DM (11)	3 (37.5%)	0 (0%)	0 (0%)	1 (100%)
HT (13)	4 (50%)	0 (0%)	0 (0%)	1 (100%)
Other (6)	1 (12.5%)	0 (0%)	2 (40%)	0 (0%)
None (29)	2 (25%)	1 (100%)	3 (60%)	0 (0%)
Bleeding site at diagnosis				
GI bleeding (4)	2 (25%)	0 (0%)	0 (0%)	0 (0%)
Intracranial hemorrhage (2)	1 (12.5%)	0 (0%)	0 (0%)	0 (0%)
Hematuria or hypermenorrhea (6)	1 (12.5%)	1 (100%)	0 (0%)	0 (0%)
Epistaxis needs to doing transfusion (1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Petechiae (28)	3 (37.5%)	0 (0%)	3 (60%)	1 (100%)
Bleeding wound (2)	1 (12.5%)	0 (0%)	0 (0%)	0 (0%)
No bleeding (8)	0 (0%)	0 (0%)	2 (40%)	0 (0%)
Severity				

	Dapsone	Azathioprine plus dapsone	Colchicine plus dapsone	Azathioprine plus colchicine
n	8	1	5	1
Mild bleeding without transfusion (33)	6 (75%)	0 (0%)	3 (60%)	1 (100%)
Bleeding with transfusion (3)	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Life threatening bleeding, hypovolemic shock (7)	2 (25%)	0 (0%)	0 (0%)	0 (0%)
No bleeding (8)	0 (0%)	0 (0%)	2 (40%)	0 (0%)
Type of ITP				
Relapsed ITP (11)	0 (0%)	1 (100%)	1 (20%)	1 (100%)
Refractory ITP (19)	3 (37.5%)	0 (0%)	3 (60%)	0 (0%)
Steroid-dependent ITP (21)	5 (62.5%)	0 (0%)	1 (20%)	0 (0%)
Steroid treatment				
No steroid (2)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
< 0.5 mg/kg/day of prednisolone or another steroid dose equivalent (26)	5 (62.5%)	0 (0%)	1 (20%)	1 (100%)
≥0.5 mg/kg/day of prednisolone or another steroid dose equivalent (23)	3 (37.5%)	1 (100%)	4 (80%)	0 (0%)
Platelet count prior to second-line treatment Median (IQR)	11,000 (5,000, 13,500)	8,000	8,000 (6,000, 16,000)	16,000

Result of treatment response

The group of patients receiving eltrombopag had a 100% complete response (CR). The group treated with splenectomy, azathioprine, colchicine, and dapsone had a total response of more than 80%, whereas the dapsone group had 62.5% of CR. The splenectomy had a CR of 57.1%6. Furthermore, the azathioprine group responded to CR by 23.1%, and colchicine responded with a CR of 36.4%. For colchicine combined with dapsone, there was an overall response of 60% with a CR response of 20%. Azathioprine plus dapsone and azathioprine plus colchicine had a total partial response (PR) And it was found that the group receiving danazol did not respond to treatment as shown in Table 2 and picture 1.

The second-line therapy in the study has different periods of increasing platelet counts and responsibility. Eltrombopag, colchicine, dapsone, azathioprine, colchicine plus dapsone, azathioprine plus dapsone, or colchicine had the quickest clinical response time within 4 weeks. For most splenectomies, the response to post-splenectomy treatment began within 5-8 weeks. This was shown in Table 2.

Following the 6-month after treatment, the platelet count level and platelet count difference (inbracket) results are as follows: eltrombopag, dapsone, colchicine, azathioprine, azathioprine plus colchicine, splenectomy, azathioprine plus dapsone, danazol, and dapsone plus colchicine are 208,500/L (182,000/L), 86,000/L (75,000/L), 84,000/L (74,000/L), 60,000/L (40,000/L), 53,000/L(37,000/L), 41,000/L), 49000/L (41,000), 26,000/L (20,000/L), and 17,000/L (11,000/L), respectively. These results were shown in Table 2.

Some second-line treatments could have caused in reducing or stopping steriodal used. The group of participants who received eltrombopag can stop using steroids by 75%. Patients who underwent splenectomy stopped taking steroids by 42.9% followed by azathioprine and colchicine groups where 38.5% and 27.3% of the patients could stop taking steroids, respectively (As shown in Table 2 and Figure 2). The difference in platelet counts between before and after second-line therapy were shown in Figure 3. We found that eltrombopag and splenectomy were most effective management in elevating platelet counts. Colchicine, dapsone, azathioprine, and combination therapy could also elevate platelet counts to above 50,000/L.

Table 2: Demonstrating second-line treatment of primary ITP and therapeutic effects

	Eltrombopag	Splenectomy	Azathioprine,	Colchicine	Danazol
n	4	7	13	11	1
Platelet count prior to second line - treatment [Median (IQR)]	26,000 (14,500, 32,000)	9,000 (4,000, 12,000)	20,000 (10,000, 30,000)	10,000 (7,000, 26,000)	6,000
Platelet count after treatment at 6 months [Median (IQR)]	208,500 (144,000, 304,500)	50,000 (21,000, 354,000)	60,000 (40,000, 150,000)	84,000 (44,000, 194,000)	26,000
Mean difference of platelet count before and after treatment at 6 months	182,000	41,000	40,000	74,000	20,000
Maximum Platelet count respond to treatment [Median (IQR)]	307,000 (242,500, 340,500)	252,000 (48,000, 354,000)	110,000 (57,000, 160,000)	100,000 (50,000,174,000)	26,000
Time to overall response within 24 weeks					
1-4 weeks (34)	4 (100%)	5 (71.4%)	10 (76.9%)	8 (72.7%)	1 (100%)
5-8 weeks (6)	0 (0%)	2 (28.6%)	0 (0%)	2 (18.2%)	0 (0%)
9-12 weeks (4)	0 (0%)	0 (0%)	2 (15.4%)	0 (0%)	0 (0%)
>12 weeks (5)	0 (0%)	0 (0%)	1 (7.7%)	1 (9.1%)	0 (0%)
Type of response					
No response (10)	0 (0%)	1 (14.3%)	2 (15.4%)	1 (9.1%)	1 (100%)
Partially response (22)	0 (0%)	2 (28.6%)	8 (61.5%)	6 (54.5%)	0 (0%)
Complete response (19)	4 (100%)	4 (57.1%)	3 (23.1%)	4 (36.4%)	0 (0%)
Overall response (41)	4 (100%)	6 (85.7%)	11 (84.6%)	10 (90.9%)	0 (0%)
Bleeding after treatment					
GI bleeding (1)	0 (0%)	0 (0%)	0 (0%)	1 (9.1%)	0 (0%)
Intracranial hemorrhage (1)	0 (0%)	0 (0%)	1 (7.7%)	0 (0%)	0 (0%)
Hematuria	0 (0%)	1 (14.3%)	1 (7.7%)	0 (0%)	0 (0%)
Petechia, and ecchymosis need to doing transfusion (18)	2 (50%)	1 (14.3%)	6 (46.2%)	2 (18.2%)	1 (100%)
Bleeding wound (1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
No bleeding (28)	2 (50%)	5 (71.4%)	5 (38.5%)	8 (72.7%)	0 (0%)
The severity bleeding afterthe treatment					
Mild bleeding without transfusion (22)	2 (50%)	2 (28.6%)	7 (53.8%)	3 (27.3%)	1 (100%)
Life-threatening bleeding, hypovolemic shock (1)	0 (0%)	0 (0%)	1 (7.7%)	0 (0%)	0 (0%)
No bleeding (28)	2 (50%)	5 (71.4%)	5 (38.5%)	8 (72.7%)	0 (0%)
Thrombosis					

	Eltrombopag	Splenectomy	Azathioprine,	Colchicine	Danazol
n	4	7	13	11	1
CVA (4)	0 (0%)	0 (0%)	2 (15.4%)	1 (9.1%)	0 (0%)
DVT (1)	1 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CVST (2)	0 (0%)	2 (28.6%)	0 (0%)	0 (0%)	0 (0%)
No thrombosis (44)	3 (75%)	5 (71.4%)	11 (84.6%)	10 (90.9%)	1 (100%)
Prednisolone discontinuation					
No steroid (14)	3 (75%)	3 (42.9%)	5 (38.5%)	3 (27.3%)	0 (0%)
< 0.5 mg/kg/days of prednisolone or another steroid dose equivalent (31)	1 (25%)	3 (42.9%)	7 (53.8%)	7 (63.6%)	1 (100%)
≥0.5 mg/kg/days of prednisolone or another steroid dose equivalent (6)	0 (0%)	1 (14.3%)	1 (7.7%)	1 (9.1%)	0 (0%)
Hepatitis					
No hepatitis (42)	4 (100%)	7 (100%)	12 (92.3%)	9 (81.8%)	1 (100%)
Transaminitis without symptoms (9)	0 (0%)	0 (0%)	1 (7.7%)	2 (18.2%)	0 (0%)
Dead within 1 year after treatment					
Alive (47)	4 (100%)	7 (100%)	13 (100%)	8 (72.7%)	0 (0%)
Thrombosis (1)	0 (0%)	0 (0%)	0 (0%)	1 (9.1%)	0 (0%)
Infection (2)	0 (0%)	0 (0%)	0 (0%)	2 (18.2%)	0 (0%)
Unknown status (1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)

Table 2: Demonstrating second-line treatment of primary ITP and therapeutic effects(continuous)

	Dapsone	Azathioprine plus dapsone	Colchicine plus dapsone	Azathioprine plus colchicine
n	8	1	5	1
Platelet count before treatment second line [Median (IQR)]	11,000 (5,000, 13500)	8,000	8,000 (6,000, 16,000)	16,000
Platelet count after treatment at 6 months[Median (IQR)]	86,000 (40,000, 110,500)	49,000	17,000 (16,000, 140,000)	53,000
Median platelet count before and after treatment at 6 months	75,000	41,000	11,000	37,000
Maximum Platelet Count response to Treatment [Median (IQR)]	141,500 (56,000, 216,000)	49,000	50,000 (24,000, 207,000)	53,000
Time to overall response within 24 weeks				
1-4 weeks (34)	4 (50%)	1 (100%)	3 (60%)	0 (0%)
5-8 weeks (6)	1 (12.5%)	0 (0%)	1 (20%)	0 (0%)
9-12 weeks (4)	2 (25%)	0 (0%)	0 (0%)	0 (0%)
>12 weeks (5)	1 (12.5%)	0 (0%)	1 (20%)	1 (100%)
Type of response				
No response (10)	3 (37.5%)	0 (0%)	2 (40%)	0 (0%)
Partially response (22)	2 (25%)	1 (100%)	2 (40%)	1 (100%)
Complete response (19)	3 (37.5%)	0 (0%)	1 (20%)	0 (0%)
Overall response (41)	5 (62.5%)	1 (100%)	3 (60%)	1 (100%)
Bleeding after treatment				
GI bleeding (1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Bleeding after treatment				

	Dapsone	Azathioprine plus dapsone	Colchicine plus dapsone	Azathioprine plus colchicine
n	8	1	5	1
Intracranial hemorrhage (1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hematuria	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Petechia, and ecchymosis need to doing transfusion (18)	4 (50%)	0 (0%)	2 (40%)	0 (0%)
Bleeding wound (1)	0 (0%)	0 (0%)	1 (20%)	0 (0%)
No bleeding (28)	4 (50%)	1 (100%)	2 (40%)	1 (100%)
The severity of bleed after treatment				
Mild bleeding without transfusion (22)	4 (50%)	0 (0%)	3 (60%)	0 (0%)
Life threatening bleeding, hypovolemic shock (1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
No bleeding (28)	4 (50%)	1 (100%)	2 (40%)	1 (100%)
Thrombosis				
CVA (4)	0 (0%)	0 (0%)	1 (20%)	0 (0%)
DVT (1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CVST (2)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
No thrombosis (44)	8 (100%)	1 (100%)	4 (80%)	1 (100%)
Prednisolone discontinuation				
No steroid (14)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
< 0.5 mg/kg/days of prednisolone or another steroid dose equivalent (31)	7 (87.5%)	1 (100%)	3 (60%)	1 (100%)
≥0.5 mg/kg/days of prednisolone or another steroid dose equivalent (6)	1 (12.5%)	0 (0%)	2 (40%)	0 (0%)
Hepatitis				
No hepatitis (42)	4 (50%)	0 (0%)	4 (80%)	1 (100%)
Transaminitis without symptoms (9)	4 (50%)	1 (100%)	1 (20%)	0 (0%)
Dead within 1 year after treatment				
Alive (47)	8 (100%)	1 (100%)	5 (100%)	1 (100%)
Thrombosis (1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Infection (2)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unknown status (1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

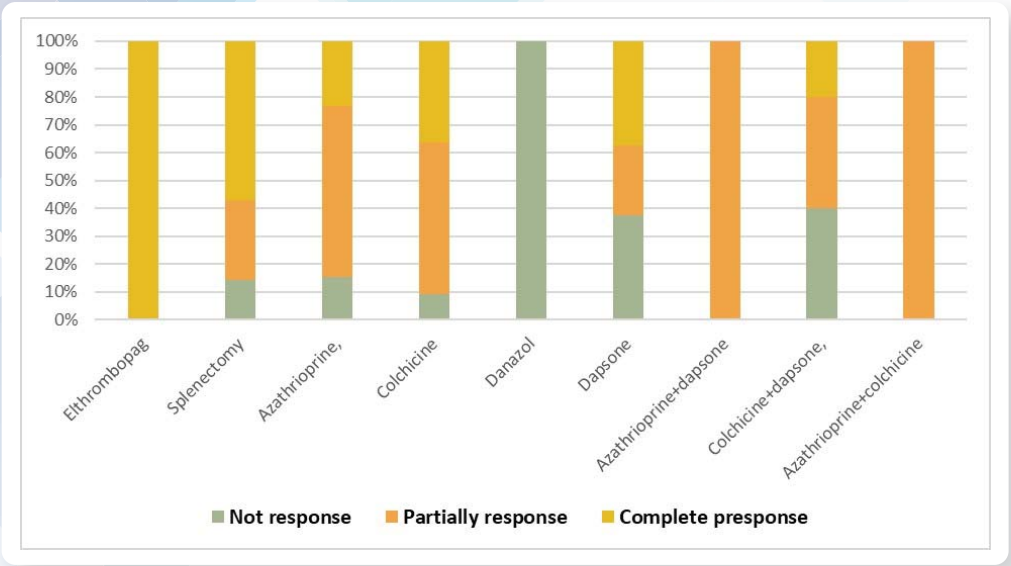
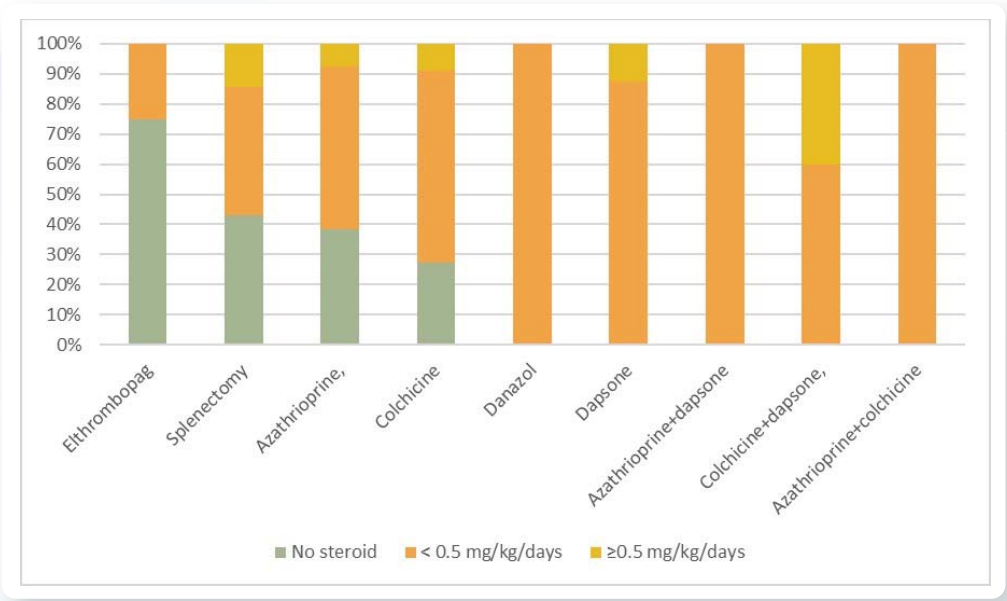
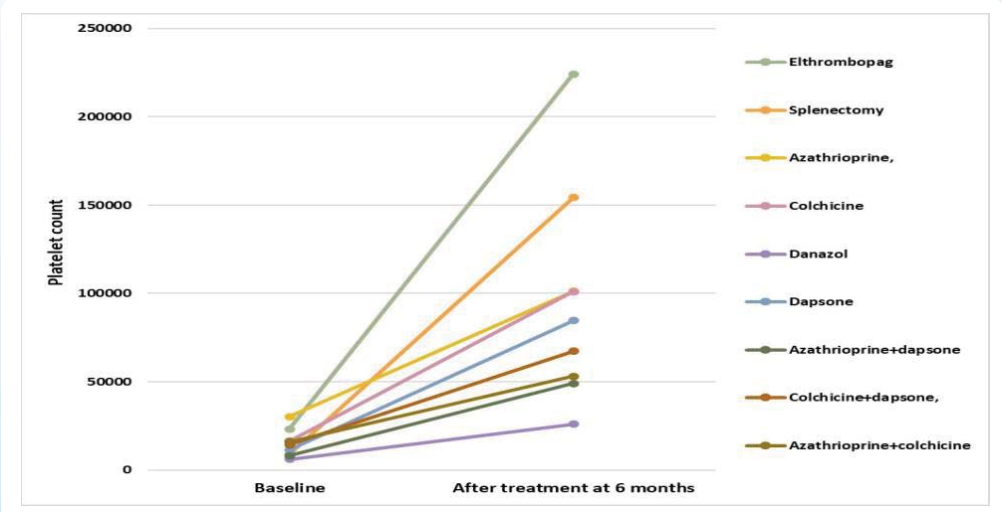


Figure 1: Demonstrating second-line ITP treatment with a response



e 2: Demonstrate second-line ITP treatment with steroids after 6 months of treatment



ure 3: Second-line ITP treatment shows the platelet count levels before a after 6 months of treatment

Regarding to treatment-related complications, abnormal post-treatment bleeding,thrombosis, death from all causes, and severe hepatitis were included. We found that treatment with eltrombopag had 50% less severe hemorrhage and also had 25% DVT less than othertreatments. Participants who underwent splenectomy had 28.6% mild hemorrhage and ischemic stroke. Azathioprine group has mild bleeding (53.8%), severe hemorrhage (7.7%), and ischemic stroke (15.4%). Colchicine had mild bleeding for 27.3% and ischemic strokes for 9.1%, which resulting in one death after one year of treatment; 18.2% died from thrombosis. Danazol has mild bleeding. Azathioprine combined with dapsone or colchicine did not show any abnormal bleeding. Colchicine combined with dapsonehad 60% mild-type bleeding, and had 20% ischemic stroke. In the study, there was no evidence of hepatitis or mild liver inflammation. These results were shown in Table 2.

Table 3: Demonstrating factor and treatment response of primary ITP

Factor associated	not response	partially response	complete response	partial or complete response	p-value		
					p vs n	c vs n	p +c vs n
Age							
· < 40 years	3 (30%)	9 (40.9%)	5 (26.3%)	14 (34.1%)	0.555	0.833	0.803
· At least 40 years	7 (70%)	13 (59.1%)	14 (73.7%)	27 (65.9%)			
Sex							
· Male	7 (70%)	17 (77.3%)	15 (78.9%)	32 (78%)	0.66	0.593	0.591
· Female	3 (30%)	5 (22.7%)	4 (21.1%)	9 (22%)			
Bleeding site before treatment							
· GI bleeding	2 (20%)	1 (4.5%)	1 (5.3%)	2 (4.9%)	0.419	0.33	0.349
· Intracranial hemorrhage	1 (10%)	0 (0%)	1 (5.3%)	1 (2.4%)			
· Hematuria	0 (0%)	2 (9.1%)	4 (21.1%)	6 (14.6%)			
· epitaxis	0 (0%)	1 (4.5%)	0 (0%)	1 (2.4%)			
· Petechia or ecchymosis	5 (50%)	13 (59.1%)	10 (52.6%)	23 (56.1%)			
· Bleeding wound	1 (10%)	1 (4.5%)	0 (0%)	1 (2.4%)			
· No bleeding	1 (10%)	4 (18.2%)	3 (15.8%)	7 (17.1%)			
Platelet count treatment second line							
< 10,000/L	7 (70%)	8 (36.4%)	5 (26.3%)	13 (31.7%)	0.144	0.059	0.064
10,000 - 30,000/L	3 (30%)	10 (45.5%)	11 (57.9%)	21 (51.2%)			
>30,000/L	0 (0%)	4 (18.2%)	3 (15.8%)	7 (17.1%)			
Severity of bleeding before treatment	6 (60%)	15 (68.2%)	12 (63.2%)	27 (65.9%)	0.184	0.721	0.33
· Mild bleeding without transfusion	0 (0%)	2 (9.1%)	1 (5.3%)	3 (7.3%)			
· Bleeding with transfusion	3 (30%)	1 (4.5%)	3 (15.8%)	4 (9.8%)			
· Life threatening bleeding, hypovolemic shock	1 (10%)	4 (18.2%)	3 (15.8%)	7 (17.1%)			
Type of ITP							
· Relapsed ITP	1 (10%)	5 (22.7%)	5 (26.3%)	10 (24.4%)	0.536	0.567	0.517
· Refractory ITP	5 (50%)	7 (31.8%)	7 (36.8%)	14 (34.1%)			
· Steroid-dependent ITP	4 (40%)	10 (45.5%)	7 (36.8%)	17 (41.5%)			
Steroid treatment at initial treatment							
· No steroid	1 (10%)	1 (4.5%)	0 (0%)	1 (2.4%)	0.306	0.24	0.239
· < 0.5 mg/kg/days of prednisolone or another steroid dose equivalent	3 (30%)	13 (59.1%)	10 (52.6%)	23 (56.1%)			

· ≥0.5 mg/kg/days of prednisolone or another steroid dose equivalent	6 (60%)	8 (36.4%)	9 (47.4%)	17 (41.5%)			
Bleeding site after treatment							
· GI bleeding	1 (10%)	0 (0%)	0 (0%)	0 (0%)	0.247	0.344	0.106
· Intracranial hemorrhage	1 (10%)	0 (0%)	0 (0%)	0 (0%)			
· Hematuria	0 (0%)	2 (9.1%)	0 (0%)	2 (4.9%)			
· Petechia or ecchymosis	3 (30%)	8 (36.4%)	7 (36.8%)	15 (36.6%)			
· Bleeding wound	0 (0%)	0 (0%)	1 (5.3%)	1 (2.4%)			
· No bleeding	5 (50%)	12 (54.5%)	11 (57.9%)	23 (56.1%)			
Severity of bleeding before treatment							
· Mild bleeding without transfusion	4 (40%)	10 (45.5%)	8 (42.1%)	18 (43.9%)	0.321	0.371	0.124
· Bleeding with transfusion	1 (10%)	0 (0%)	0 (0%)	0 (0%)			
· Life threatening bleeding, hypovolemic shock	5 (50%)	12 (54.5%)	11 (57.9%)	23 (56.1%)			
Steroid treatment after treatment 6 month							
· No steroid	2 (20%)	3(13.6%)	9 (47.4%)	12 (29.3%)	0.646	0.149	0.556
· < 0.5 mg/kg/days of prednisolone or another steroid dose equivalent	4 (40%)	17 (77.3%)	10 (40%)	27 (65.9%)	0.040*	0.518	0.133
· ≥0.5 mg/kg/days of prednisolone or another steroid dose equivalent	4 (40%)	2 (9.1%)	0 (0%)	2 (4.9%)	0.038*	0.003*	0.002*
Treatment					0.406	0.319	0.298
· Eltrombopag	0 (0%)	0 (0%)	4 (21.1%)	4 (9.8%)	N/A	0.118	0.304
· Splenectomy	1 (10%)	2 (9.1%)	4 (21.1%)	6 (14.6%)	0.935	0.454	0.703
· Azathioprine	2 (20%)	8 (36.4%)	3 (15.8%)	11 (26.8%)	0.355	0.775	0.657
· Colchicine	1 (10%)	6 (27.3%)	4 (21.1%)	10 (24.4%)	0.273	0.454	0.321
· Danazol	1 (10%)	0 (0%)	0 (0%)	0 (0%)	0.132	0.161	0.041*
· Dapsone	3 (30%)	2 (9.1%)	3 (15.8%)	5 (12.2%)	0.131	0.369	0.165
· Azathioprine and dapsone	0 (0%)	1 (4.5%)	0 (0%)	1 (2.4%)	0.493	N/A	0.618
· Colchicine and dapsone	2 (20%)	2 (9.1%)	1 (5.3%)	3 (7.3%)	0.387	0.216	0.227
· Azathioprine and colchicine	0 (0%)	1 (4.5%)	0 (0%)	1 (2.4%)	0.493	N/A	0.618

The factors influenced in the response rate to the treatment of idiopathic ITP patientsreported that age, sex, type of ITP, and corticosteroid level were combined with the second therapy, the severity of bleeding or bleeding site had no effect on the response of plateletcount levels or the significance of the statistical analysis as shown in Table 3.

Discussion

Second-line therapy study in idiopathic ITP patients reported that eltrombopag,colchicine, dapsone, azathioprine, and the use of azathioprine in combination with dapsone or colchicine had a better overall response of more than 80%. In this study, all ITP patients who received eltrombopag had 100% complete responses. Furthermore, eltrombopag could increase the highest platelet count levels after 6 months of treatment, compared to another type of treatment. Eltrombopag caused less serious side effects such as thrombosis compared to splenectomy. This study did not find any significant association between platelet count and age, sex, steroid therapy as well as the type of treatment received.

The systematic review assessed several treatments used for adult ITP in the second-line setting.Similar to this study, most patients were treated with splenectomy followed byrituximab, eltrombopag, azathioprine, colchicine, and dapsone. The results of the systematic

review found that eltrombopag increased the platelet count levels to more than 50,000/L, or the platelet count levels could double compared to before treatment. The eltrombopag produced a total response at 6 months as much as 100%, that finding was consistent with previous meta-analysis.[6] This meta-analysis reported that the mean of the total response rate reaches 86.5% in the group treated with splenectomy consistent with splenectomy treatment, in our study the total response was 85.7 percent. The period during which the platelet count began to rise above 30,000/L had varied time periods. [6] From two weeks after the splenectomy, or approximately 22–29 daysafter the splenectomy. [7,12,13] In this study, 71.4% of patients had increased platelet count of more than 30,000/L within 4 weeks, and 28.6% began a rise in platelet count from 5 to 8 weeks after splenectomy.

For azathioprine, this study found a total response of 85%. The response was similar to the previous report in the Second-Line Therapy for Immune Thrombocytopenia [14]: In a phase 4 study conducted in Canada, 75% of patients responded to azathioprine. For other types of treatment, dapsone provided an 84% overall response in our study which was higher than the finding from the Syed study [9], which found a 54.8% response after taking dapsone and didn't experience severe side effects such as methemoglobinemia, neuropathy, and rash. Colchicine had a total response of 90% and had a quick response interval time. 72.7% of patients began to respond within 1 to 4 weeks after taking the drug, which was a very good response compared to the Strother SV study [10], which found a post-colchicine response of only 29%. We didn't find the efficacy of danazol on 2nd line treatment of ITP. This finding wasn't similar to the finding from the effect of danazol in primary ITP from a single center in China study that found that danazol was overall response of 65%. [15]

Combination therapies for ITP used in this study included azathioprine plus colchicine, colchicine plus dapsone, and azathioprine plus dapsone. Although the drug combinations provided a good overall response rate, there was a relatively small population for each drug combination. A previous study reported the effectiveness of colchicine in combination with dapsone. Such a study was conducted on 64 participants previously treated for ITP. It reported that the patients had a total response of 82.8% and CR of 75% within 8 weeks after such combination treatments. [16] However, there was an overall response of 60% and a CR of 20% in this study given that only 5 patients received both medicines. We found a faster response compared to the previously mentioned study by starting to respond within 1 to 4 weeks. There was no association between treatment response and available factors such as age, steroid use, and types of treatments.

For the treatment of azathioprine combined with colchicine and azathioprine combined with dapsone, there was a population receiving such medication per 1 person in each arm. Everyone had a PR response but information about the efficacy of such combinations was limited.

Treatment with colchicine, dapsone, azathioprine, or the combination of the two drugs as described above is interesting because it has been found to have a lot of response totreatment. Side effects or bleeding are less common, and thrombosis is a low-incident of events as well as cheaper than eltrombopag. Patients who underwent splenectomy responded very well either in this study or in previous studies with fewer bleeding episodes. Although, there may be surgical side effects associated with more infections than usual and more abnormal blood eruptions.(6,9,12) The use of eltrombopag responded well but was expensive. Alternative second-line treatment of idiopathic ITP is colchicine, dapsone, and azathioprine in the Saraburihospital context.

Conclusion

The results of the study found that the treatment with azathioprine, colchicine, and dapsone, the combination therapies, was effective and had a good response. The effect was less severe bleeding; less abnormal bleeding occurred. The treatment as above was low cost. Splenectomy is also used as a second-line treatment for idiopathic ITP, the response is positive, but the side effects include venous thrombosis. And the use of eltrombopag has a great response, but there may be limitations on treatment rights and costs. Alternative second-line treatment of idiopathic ITP is
colchicine, dapsone, and azathioprine in the Saraburi hospitalcontext.

This research had the distinctive point that the study on primary ITP in Saraburi patients could be applied in Saraburi Hospital, and the azathioprine, colchicine, and dapsone study in second-line ITP patient management was limited, so this study had data for another research project and supportive data for alternative second-line treatment. This study has the following limitations: a low number of studied populations. More populations for study are needed to produce references based on the majority of the population. The short duration of the study made it impossible to evaluate long-term effects, such as bleeding mortality and blood test response, as in the previous study.In the next study, the authors plan to increase the population of the study from multicenter data in hospitals in Thailand. For example, consider response outcomes over a period of 1-3 years and mortality rates. Side effects of drug use

reducing response times require additional third-line treatment, and further studies may be an RCT comparing intergroup treatments such as azathioprine, colchicine, dapsone, or combination therapy with eltrombopag, etc.

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