







ORIGINAL ARTICLE

Treatment of immune thrombocytopenia in Australian adults: A multicenter retrospective observational study

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Abstract

Background: In Australia, prescribing restrictions limit access to internationally recommended second-line therapies such as rituximab and thrombopoietin agonists (TPO-A) (eltrombopag and romiplostim). Subsequent lines of therapy include an array of immunosuppressive and immune-modulating agents directed by drug availability and physician and patient preference.

Objectives: The objective of the study was to describe the use of first and subsequent lines of treatment for adult immune thrombocytopenia (ITP) in Australia and to assess their effectiveness and tolerability.

Patients/Methods: A retrospective review of medical records was conducted of 322 patients treated for ITP at eight participating centers in Australia between 2013 and 2020. Data were analyzed by descriptive statistics and frequency distribution using pivot tables, and comparisons between centers were assessed using paired *t* tests.

Results: Mean age at diagnosis of ITP was 48.8 years (standard deviation [SD], 22.6) and 58.3% were women. Primary ITP was observed in 72% and secondary ITP in 28% of the patients; 95% of patients received first-line treatment with prednisolone (76%), dexamethasone (15%), or intravenous immunoglobulin (48%) alone or in combination. Individuals with secondary ITP were less steroid dependent (72% vs. 76%) and required less treatment with a second-line agent (47% vs. 58%) in the study sample. Over half (56%) of the cohort received treatment with one or more second-line agents. The mean number of second-line agents used for each patient was 1.9 (SD, 1.2). The most used second-line therapy was rituximab, followed by etrombopag and splenectomy. These also generated the highest rates of complete response (60.3%, 72.1%, and 71.8% respectively). The most unfavorable side effect profiles were seen in long-term corticosteroids and splenectomy.

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Conclusion: A wide range of “second-line” agents were used across centers with variable response rates and side effect profiles. Findings suggest greater effectiveness of rituximab and TPO-A, supporting their use earlier in the treatment course of patients with ITP across Australia.

KEYWORDS

Australia, idiopathic, immunosuppression, observational study, purpura, therapy, thrombocytopenic

Essentials

- We reviewed the treatment of 322 Australian adults with immune thrombocytopenia from 2013 to 2020.
- Treatment failure was common, and second-line agents varied in effectiveness and tolerability.
- Long-term corticosteroids and splenectomy were associated with significant side effects.
- Thrombopoietin agonists and rituximab were effective and well tolerated, but access was limited.

1 | INTRODUCTION

Immune thrombocytopenia (ITP) is a disorder characterized thrombocytopenia, which can be self-limiting, chronic, or relapsing/remitting. Thrombocytopenia ensues following platelet destruction that is mediated by the production of platelet-specific IgG (most commonly targeting platelet α IIb β 3 and glycoprotein Ib-IX) by B lymphocytes, as well as reduced platelet production secondary to T-lymphocyte-mediated platelet and megakaryocyte cytotoxicity.¹ Bleeding complications are infrequent with platelet counts above $30 \times 10^9/L$, and this level is commonly used as a threshold for treatment.² First-line therapies usually comprise corticosteroids plus or minus intravenous immunoglobulin (IVIG). Beyond first line, a gamut of drugs (thrombopoietin agonists [TPO-As], rituximab, danazol, dapsone, mycophenolate mofetil, cyclosporine A, azathioprine, cyclophosphamide) are available to clinicians, most of which have a very limited evidence base in treating ITP. These drugs are generally characterized by modest response rates and a variety of side effects that may necessitate drug discontinuation.³ In Australia, patients' ability to access medications is governed by the Therapeutic Goods Administration (TGA), which evaluates and approves drugs for prescription. Drugs not registered with the TGA can be accessed in the context of clinical trials or by special application by a prescriber.⁴ A separate organization, the Department of Health, administers the Pharmaceutical Benefits Scheme (PBS), which governs subsidized access to medications and specifies indications for which drugs can be prescribed at subsidized rates.⁵ In practice, the choice of second-line agents for the treatment of ITP is governed by drug availability within health care systems, physician choice and experience with specific medications, and patient preference and side effect profile of each of the medications.

Guidelines published by the American Society of Hematology (ASH),² as well as subsequent updates^{2,6} recommend the use of TPO-As or rituximab as second-line options after relapse following first-line agents. These medications are not easily accessible in

Australia due to limitations placed on clinicians through the PBS. Clinicians in most Australian centers therefore use alternate second-line agents (mentioned above).

In the current 2019 ASH guidelines published by Neunert and colleagues,² the panel reported that formal recommendations regarding other (excluding TPO-As and rituximab) second-line agents were not made because research since the 1996 guideline had been inadequate to allow evidence-based recommendations on appropriate indications or timing. Since the release of this guideline, evidence regarding use of these alternate second-line agents has been published and includes predominantly single-center experiences with single agents.⁷ Similarly, the updated international consensus report on the investigation and management of primary immune thrombocytopenia by Provan and colleagues does not make recommendations regarding choice of second-line agents other than TPO-As, rituximab, and splenectomy.⁸ This study reviews the use of these second- and successive-line therapies and their efficacies from multiple hospitals around Australia.

2 | MATERIAL AND METHODS

2.1 | Study design

The objective of the study was to describe the use of first and subsequent lines of treatment for adult ITP in Australia and to assess their effectiveness and tolerability. A retrospective study was conducted of patients who were treated for ITP by hematologists at eight participating centers in Australia between 2013 and 2020. Sites included five large tertiary metropolitan hospitals across three states: the Princess Alexandra Hospital (PAH) (Brisbane, Queensland); the Royal North Shore Hospital (RNSH), Westmead Hospital (WH), and Concord Repatriation Hospital (CRH) (Greater Sydney Region, New South Wales); and the Royal Adelaide Hospital (RAH) (Adelaide, South Australia). Centers also included two

medium tertiary metropolitan hospitals, Nepean Hospital (NH) and Blacktown Hospital (BH) (Greater Sydney Region), and one tertiary regional referral center, Lismore Base Hospital (LBH) (Northern New South Wales). All research was approved by the Northern Sydney Human Research Ethics Committee (2019/ETH09804).

2.2 | Patient inclusion and data collection

All patients aged 18 years and older who received a diagnosis of ITP and/or had been treated for ITP at participating centers during the study period (2013–2020) were included in the study. Exclusion criteria included incomplete medical records preventing accurate data collection. The study sample included all patients at participating sites meeting inclusion criteria and so separate quantification of sample size and power were not conducted.

At four sites (LBH, NH, CRH, and RAH), patients were identified by record inquiry based on their diagnosis as per the International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) diagnostic code system. Charts were reviewed for all patients presenting to the hospital during the study period (2013–2020) receiving an ICD-10 diagnostic code D69.6 (thrombocytopenia)⁹ or D69.3 (immune thrombocytopenic purpura).⁹

In the remaining four centers (RNSH, PAH, and WH /BH), patients were identified by review of clinic notes and departmental records by participating hematologists at those sites.

Details of treatment strategies and response to treatment were obtained by review of patient medical records. Treatment and response data were collected retrospectively for the entire study period, including the duration of follow-up with the treating hematologist. Due to the nature of the data available, it was not universally possible to determine the reason for the cessation of follow-up; therefore, loss to follow-up was not captured separately. Data collection was undertaken using the purpose-built web-based Research Electronic Data Capture database,¹⁰ accessible by researchers at each study site (see Appendix S1 for data collection tool). For the purposes of this study, definitions of disease severity,

quality of response, and duration of response were as established in the Vicenza Consensus Conference Standardization of Terminology, Definitions, and Outcome Criteria in Immune Thrombocytopenic Purpura of Adults and Children (Appendix S2).¹¹

2.3 | Statistical analysis

All data were fully anonymized before assessment. Data compilation and calculation of descriptive statistics including frequency and percentage distribution across multiple variables were done using Microsoft Excel, primarily using functions of pivot tables.

Paired *t* tests (two-sample assuming equal variances) were used to assess differences in treatments and outcomes between participating centers. A *p*-value threshold of less than 0.05 was used to define statistically significant differences in demographics, duration of hospitalization, platelet counts, and duration of treatment.

Where patient treatment did not correspond to available response options in the data collection tool (see Appendix S1), free-text data were entered during data collection and analyzed manually by the research team. Statistical analysis was not applied for these subgroups due to the limited sample size.

3 | RESULTS

3.1 | Patient population

The study population (Table 1) comprised 322 individuals with a mean age at diagnosis of 48.8 years and SD of 22.6 years. Of these patients, 58.3% were women. The mean age of patients at presentation was similar across participating centers except for PAH and WH, at which patients were significantly younger (mean age, 39.8 years; SD, 17.0; and mean age, 41.3 years; SD, 17.8; *p* = 0.007 and *p* = 0.01, respectively) compared to other participating centers.

Mean platelet count at presentation to hospital was 13.4×10^9 cells/L (SD, 16.9×10^9 cells/L) and did not differ

TABLE 1 Patient population

Treating center	Female (%)	Number of patients	Mean age at diagnosis (SD)	Mean (SD) duration of hospitalization (days)	Mean (SD) platelet count at presentation ($\times 10^9$ cells/L)
Blacktown Hospital	N/A	11	N/A	14.6 (24.1)	14.8 (13.5)
Lismore Base Hospital	65.8	38	46.1 (30.4)	6.7 (5.2)	15.9 (24.5)
Nepean Hospital	52.0	25	54.5 (21.9)	7.3 (6.4)	12.0 (16.4)
The Concord and Repatriation Hospital	58.0	76	54.2 (20.7)	6.0 (6.6)	15.8 (21.0)
The Princess Alexandra Hospital	65.5	59	39.8 (17.0)	6.0 (3.9)	9.9 (9.0)
The Royal Adelaide Hospital	45.2	31	56.1 (19.0)	7.2 (6.9)	11.0 (12.8)
The Royal North Shore Hospital	48.4	36	52.7 (25.3)	6.0 (5.1)	15.8 (15.6)
Westmead Hospital	66.7	46	41.3 (17.8)	6.4 (10.5)	13.1 (14.1)
Total	58.3	322	48.8 (22.6)	6.6 (7.8)	13.5 (16.9)

Abbreviations: N/A, not applicable; SD, standard deviation.

TABLE 2 Etiology and treatment outcomes of secondary ITP

Secondary etiology	Number of Patients	Average age at diagnosis, mean (SD)	Female (%)	Bleeding at presentation (%)	Average duration of hospitalization (days), mean (SD)	Average duration of prednisone treatment (days), mean (SD)	Steroid dependent (n)	Required second-line agent (%)	Required third-line agent (%)	Required fourth-line agent (%)	Required fifth-line agent (%)	Additional treatment required beyond 5 lines (%)
Antiphospholipid syndrome	7	38.00 (14.18)	83.33	42.86	7.71 (2.81)	152 (180)	57	71	14	14	14	14
<i>Helicobacter pylori</i>	4	47.75 (10.14)	75.00	50.00	7.33 (6.11)	39 (44)	75	25	0	0	0	0
Hematological malignancy	11	69.10 (21.71)	30.00	45.45	8.90 (7.06)	70 (68)	73	45	18	0	0	0
Infection	27	48.96 (23.40)	45.83	59.26	5.54 (5.78)	167 (226)	74	30	7	4	0	0
Other	21	53.79 (22.55)	68.42	38.10	11.00 (16.41)	467 (971)	71	62	29	10	10	10
SLE	18	37.83 (17.98)	66.67	38.89	5.64 (2.62)	290 (425)	78	56	33	6	0	0
All secondary etiologies	88	48.85 (22.58)	58.30	43.79	6.64 (7.78)	237 (484)	73	48	20	6	3	3
All primary ITP	234	48.39 (22.63)	51.28	42.73	6.44 (7.72)	233 (462)	76	58	29	15	7	0

Drug reactions, pregnancy, connective tissue and non-SLE autoimmune disease.

Abbreviations: ITP, immune thrombocytopenia; SD, standard deviation; SLE, systemic lupus erythematosus.

significantly across centers. Of patients included in this study, 91% had either platelet counts less than 30 at presentation or bleeding at presentation mandating hospitalization, meeting the criteria for severe ITP.⁹

Mean duration of hospitalization across all centers on presentation was 6.4 days (SD, 7.8). Duration of hospitalization was similar between participating centers apart from BH where mean duration of hospitalization was 14.6 days (SD, 24.1). This was significantly greater than hospital stays at Concord ($p = 0.02$), Princess Alexandra ($p = 0.01$), and Royal North Shore Hospital ($p = 0.046$).

3.2 | Etiology of ITP

Of the patients included in the study, 234 of 322 (72%) had primary ITP, with 88 of 322 (28%) having secondary ITP. Secondary etiologies in order of prevalence were infection (i.e., all infectious etiologies other than *Helicobacter pylori*) 8.3%, other 6.5%, systemic lupus erythematosus (SLE) 5.6%, hematological malignancy 3.4%, antiphospholipid syndrome 2.1%, *H. pylori* 1.2% (Table 2). Patients with secondary ITP had a 17% greater mean duration of hospitalization (7.5 vs. 6.4 days) (Table 2). The secondary etiology with the greatest mean duration of hospitalization was "other," including drug reactions, pregnancy, connective tissue, and non-SLE autoimmune disease.

In comparison to primary ITP, study participants with a secondary etiology were less likely to receive treatment with a second-line agent (47% vs. 58%) and less likely to receive third-line (20% vs. 29%), fourth-line (5% vs. 14%), and fifth-line treatment (3% vs. 6.8%) (Table 2).

Patients with secondary ITP required fewer lines of treatment (mean, 1.8 lines of treatment; SD, 1.1) than patients with primary ITP (mean, 2.1; SD, 1.3), but this was not statistically significant ($p = 0.053$).

3.3 | Initial treatment of ITP

Initial treatment strategies are shown in Table 3. Of the 322 patients included in the study, 15 received no treatment on initial presentation. This group had a lower average age at diagnosis (mean age, 36.9 years; SD, 32.4; $n = 15$) compared to the patients receiving treatment at presentation (mean age, 49.7 years; SD, 21.9; $n = 307$), as well as a higher platelet count at presentation (mean platelet count, 39.2×10^9 cells/L), lower incidence of bleeding at presentation (6.7% vs. 43.8%), and shorter duration of hospitalization (1.6 days vs. 6.6 days) compared to those that required treatment at presentation.

The majority (95.3%) of patients in the study population presenting to hospital with newly diagnosed ITP received treatment. This group ($n = 307$) had a mean platelet count of 12×10^9 cells/L (SD, 15×10^9 cells/L).

The incidence of bleeding symptoms at presentation was 45.3% among patients receiving treatment on initial presentation. Patients

TABLE 3 Initial treatment of ITP

Initial treatment	Number of patients	Average age at diagnosis	Male patients (%)	Bleeding at presentation (%)	Average platelet count at presentation ($\times 10^9/L$)	Average duration of hospitalization (days)	Average duration of response (months)
Prednisone alone	125	45.8	33	36	14.6	5.7	16.9
Dexamethasone alone	20	48.2	45	55	11.0	5.3	9.8
IVIg alone	17	47.9	29	29	28.4	6.2	9.0
Prednisone and dexamethasone	6	35.0	17	83	5.0	6.5	8.8
Prednisone and IVIG	111	55.6	38	51	9.6	8.3	14.0
Dexamethasone and IVIG	23	45.4	48	52	6.1	6.4	6.7
Prednisone, dexamethasone and IVIG	5	48.7	20	100	3.6	5.3	1.0
All patients receiving treatment	307	49.5	36	46	12.3	6.7	13.8
No treatment	15	36.9	58	7	39.2	3.3	1.0
Total	322	49.0	42	43	13.5	6.6	13.7

Abbreviations: ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin.

TABLE 4 Initial corticosteroid prescribing patterns when used for initial treatment of ITP

Treating center	Average of platelet count at presentation ($\times 10^9$ cells/L), mean (SD)	Number of initial treatments with prednisone	Average duration of prednisone treatment (days), mean (SD)
Blacktown Hospital	14.8 (13.5)	11	266.9 (303.4)
Lismore Base Hospital	15.9 (24.5)	38	124.4 (179.1)
Nepean Hospital	12.0 (16.4)	25	191.7 (335.9)
The Concord and Repatriation Hospital	15.8 (21.0)	76	278.5 (477.12)
The Princess Alexandra Hospital	9.9 (9.0)	59	155.3 (507.0)
The Royal Adelaide Hospital	11.0 (12.8)	31	53.8 (39.8)
The Royal North Shore Hospital	15.8 (15.6)	36	432.9 (572.5)
Westmead Hospital	13.1 (14.1)	46	329.2 (701.4)
Total	13.5 (16.9)	322	237.3 (484.0)

Abbreviations: ITP, immune thrombocytopenia; SD, standard deviation.

with bleeding symptoms at presentation had a statistically significantly greater mean duration of hospitalization of 6.8 days (SD, 8.4) compared to 4.80 days (SD, 6.8) to those without bleeding symptoms ($p = 0.01$ on paired t test). Bleeding at presentation was noted in more patients with ITP secondary to infection (59.3%), *H. pylori* (50%), and hematological malignancy (45.5%) compared to average (43.5%). Initial treatment dosage was in accordance with contemporary treatment guidelines^{2,8} – that is, prednisone 1 mg/kg up to 80 mg daily for 1–4 weeks with subsequent wean, dexamethasone 40 mg po or iv daily for 4 days with up to three repeat courses as needed, IVIG 0.4–1 g/kg per dose iv (1–5 doses).^{2,8}

Prednisone monotherapy was the most common first-line treatment among patients in the study population (Tables 3,4). Mean age at diagnosis and duration of hospitalization were not significantly different between patients receiving prednisone monotherapy and all patients receiving first-line treatment. The average duration of prednisone treatment for all patients was 237 days, and there

was significant variation in duration of prednisone treatment between participating centers. Adverse effects from treatment with prednisone were noted among 141 of 247 (57.1%) of participants. Hyperglycemia and metabolic effects were most common (33.6%) followed by effects on mood (23.9%), insomnia (20.6%), hypertension (9.7%), and dermatological effects (8.1%).

Dexamethasone monotherapy was used in 20 patients with a mean age of 48.2 years (SD, 18.5; Table 3). In comparison to the total population of patients receiving treatment, these individuals had no statistically significant difference in age ($p = 0.7$), platelet count ($p = 0.8$), or duration of hospitalization ($p = 0.5$). Of the 54 patients who received dexamethasone either alone or in combination with other drugs, 29 (53%) required repeated doses to maintain response. Adverse effects from treatment with dexamethasone were seen in 31.5% (17/54) patients. Hyperglycemia and metabolic effects were most common (18.5%) followed by insomnia (11.1%) and mood-related effects (9.3%).

TABLE 5 Medications used after initial therapy of ITP

Drug	n (all lines)	Dosing	Mean (SD) time to response (days)	Mean Duration of response (months)	% Using Adjunct prednisone	Mean (SD) time to adjunct prednisone (days)	Mean (SD) duration of adjunct prednisone (months)	Complete response	No response	% Experiencing adverse Events	Proportion used second-line	
Azathioprine	23	100mg daily	26.7 (17.7)	25 (36.5)	26%	14 (19.1)	6.3 (4.0)	34.8	39.1	26.1	13.0	65.2
Combination/Other (specify)	54	N/A	19.8 (36.7)	13.25 (16.0)	68	19.6 (43.2)	14.1 (16.3)	51.9	37.0	11.1	33.3	63.0
Cyclophosphamide	2	N/A	N/A	4	0	N/A	N/A	0	50	50	50	0
Danazol	1	200mg daily	79	56	0	N/A	N/A	100	100	0	0	100
Dapsone	35	100mg daily	21.3 (37.2)	10.9 (11.7)	43	9.3 (10.0)	11.1 (11.0)	40	25.7	28.6	25.7	54.3
Dexamethasone	13	40 mg daily×4days	5.1 (2.0)	6.1 (10.8)	N/A	N/A	N/A	23.1	69.2	7.7	46.2	69.2
Eltrombopag	43	50mg daily	18.6 (20.3)	28.3 (19.7)	37	11.2 (3.8)	28.4 (16.0)	72.1	23.3	4.7	11.6	46.5
Mycophenolate	10	500mg twice daily	32.6 (13.5)	13.2 (12.5)	20	28	13 (9.9)	30%	60	30	10	80
Rituximab	63	100mg weekly×4 weeks	25.2 (13.2)	24.1 (23.6)	35	15.7 (15.8)	17.8 (17.4)	60.3	15.9	20.6	6.4	52.4
Romiplostim	37	1–5 µg/kg	13 (11.6)	62.0 (30.0)	35	12.7 (8.0)	7.8 (10.9)	59.46	18.92	18.92	16.22	35.14
Splenectomy	39	n/a	2.3 (1.8)	38.4 (39.2)	35	8.7 (15.1)	32.3 (26.6)	71.79	17.95	10.26	33.33	64.10

Abbreviations: N/A, not applicable; SD, standard deviation.

TABLE 6 Medication adverse effects

Agent	Number of patients on drug	Allergy	Anxiety	Dermatological	Fatigue	Headache	Infection	Infusion reaction	Joint pain	Mood-related	Muscle pain	Myelosuppression	Nausea	Neuropathy	Sleep disturbance	Other
Azathioprine	23	0	0	0	0	0	0	0	0	0	0	0	2	0	0	2
Combination/Other	54	2	0	6	5	4	2	0	1	2	1	1	1	0	3	8
Cyclophosphamide	2	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Danazol	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dapsone	35	0	0	1	1	2	1	0	0	0	0	0	0	0	0	9
Dexamethasone	13	0	1	0	0	2	0	0	1	1	1	0	0	0	2	2
Eltrombopag	43	0	0	2	5	4	0	0	2	0	4	0	2	0	0	2
Mycophenolate	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Rituximab	63	0	1	0	0	1	1	3	0	0	0	0	0	0	0	1
Romiplostim	37	0	0	0	1	2	1	0	1	1	2	0	2	0	0	4
Splenectomy	39	0	0	0	1	0	8	0	0	0	0	0	1	0	0	6

Comparison of first line therapy groups (prednisone vs. dexamethasone, prednisone vs. IVIG, combinations) in terms of platelet count, age at presentation, incidence of bleeding at presentation and duration of hospitalization did not yield statistically significant conclusions due to small sample sizes and wide confidence intervals.

3.4 | Medications used after initial treatment of ITP

Among included patients, 141 (44%) experienced sustained response to first-line treatment and did not require treatment with a second-line agent during the study period. Eighty-nine patients (27%) experienced sustained response to second-line treatment and did not require further lines of therapy. Forty-seven patients (15%) experienced sustained response after three lines of therapy, 22 (7%) after four lines, 7 (2%) after five lines. Twelve patients (4%) required more than five lines of treatment.

Rituximab was used as subsequent therapy in 63 patients (Table 5), where it was employed second line in 52.38% of these individuals (Table 5). The most employed dosing strategy was low-dose rituximab 100mg weekly for 4 weeks. A complete response was observed in 60.3% of cases (Table 5). The mean time to response for all patients receiving rituximab was 25.2 days (SD, 13.2) and the mean duration of response was 24.1 months (SD, 23.6). Thirty-five percent of this group (22/63) received adjunct corticosteroids. These individuals had a shorter mean time to response (15.7 days; SD, 15.8 vs. 29.6 days; SD, 9.5) and duration of response (17.8 months; SD, 17.4 vs. 26.9 months; SD, 26.1) compared to patients receiving rituximab alone. Six percent of patients experienced adverse events from rituximab, most commonly headache, and only one infusion reaction was reported (Table 6).

Eltrombopag was used in 43 patients (Table 5). Of these individuals, 46.5% received eltrombopag as second-line therapy (Table 5). The most frequently used dosage was 50mg daily (Table 5). A completed response was achieved in 72.1% (Table 5). For all patients receiving eltrombopag, the mean time to response was 16.6 days (SD, 17.6) and the mean duration of response was 28.3 months (SD, 18.4). Adjunct corticosteroids were used in 16 of 43 (37%) patients with a mean duration of prednisone wean of 222 days. Patients receiving adjunct corticosteroids had a shorter mean time to response of compared to those receiving eltrombopag only (11.2 days; SD, 3.8 vs. 18.6 days; SD, 20.3), however, mean duration of response was not significantly different between these two groups (mean duration of response 28.4 months; SD, 16.0 vs. 28.3 months; SD, 19.7, respectively). Five of 43 (12%) of patients reported adverse events, predominantly headache, fatigue, and joint/muscle pain (Table 6).

Romiplostim was used less commonly than eltrombopag, being employed in 37 patients (Table 5). It was only used second line in 35.1% of these cases (Table 5). A complete response to treatment was recorded in 59.5%. For all patients receiving romiplostim, mean time to response was 13 days (SD, 11.6) and mean duration of response was 58.5 months (SD, 25.5). Thirty-five percent (13/37) of these patients received prednisone as an adjunct with a mean

duration of prednisone wean of 773 days. These patients did not have shorter average times to response compared to patients receiving romiplostim only (12.7 days; SD, 8.0 vs. 8.7 days; SD, 2.9) but did have significantly shorter mean durations of response compared to those patients (7.8 months; SD, 10.9 vs. 62 months; SD 30.0). Sixteen percent of patients experienced adverse effects from romiplostim that included headache, muscle pain, and nausea most reported (Table 6).

Splenectomy was undertaken as a treatment strategy in 39 patients (Table 5) and was performed as a second-line option in 64.1% of these cases (Table 5). The average time to response for all patients undergoing splenectomy was 4.5 days (SD, 9.2) and average duration of response was 36.0 months (SD, 34.3). Fourteen patients received adjunct corticosteroids with a mean duration of 32 days. Among patients receiving adjunct steroids the mean time to response was 8.7 days (SD, 15.1) and the mean duration of response was 32.3 months (SD, 26.6). Patients receiving splenectomy alone had a mean time to response of 2.3 days (SD, 1.8) and a mean duration of response of 38.4 months (SD, 39.2). Thirty-six percent of patients experienced adverse events following splenectomy, with infection being the most common (Table 6).

Dapsone was the fifth most commonly used agent; it was used in 35 patients, 54.3% of whom received the drug as a second-line option (Table 5). Dosage was 100 mg daily in 32 patients, 75 mg daily in 2 patients, and 50 mg daily in 1 patient. The average time to response for all patients receiving dapsone second line was 21.3 days (SD, 37.2), and average duration of response was 10.9 months (SD, 11.7). Fifteen patients received adjunct corticosteroids, which appeared to shorten time to response significantly quicker than those who received dapsone as second agent alone (mean time to response, 9.3 days; SD, 10.0 vs. 30.3 days; SD, 47.8, respectively). Adjunctive corticosteroid therapy had a mean duration of wean of 119 days. Individuals treated with adjunctive steroids did not have a significantly different duration of response compared to those treated with dapsone only (mean duration of response, 10.3 months; SD, 13.8 vs. 11.1 months; SD, 11.0, respectively). Adverse events were reported in 26% of patients treated with dapsone (Table 6). These appeared to be dose related, being reported only in patients taking 100 mg of dapsone daily. The most reported events included fatigue and dyspnea. Only one report of oxidative hemolysis was cited.

Azathioprine was used as therapy after initial therapy in 23 patients (Table 5). This was chosen as a second-line option in 65.2% (Table 5). Twenty of 23 patients were treated with 100 mg daily, the remaining 3 patients received 50 mg daily. The mean time to response for all patients receiving azathioprine treatment was 26.7 days (SD, 17.7) with a mean duration of response of 25 months (SD, 36.5). Twenty-six percent of patients (6/23) received adjunct corticosteroids in addition to azathioprine. These patients had a shorter time to response than patients receiving azathioprine only (mean time to response, 14 days vs. 31 days; SD, 19.1, respectively). Patients receiving adjunct corticosteroids had significantly shorter overall durations of response (mean duration of response,

6.3 months; SD, 4.0 vs. 39 months; SD, 45.4). Thirteen percent (3/23) of patients experienced adverse events from azathioprine, most commonly nausea. As for dapsone, all adverse events were only experienced in patients on a relatively higher dose of azathioprine, 100 mg daily (Table 6).

Dexamethasone pulse of 40 mg daily for a duration of 4 days was used as a subsequent line of therapy in 13 patients (Table 5). It was used second line in 69.2% of these cases (Table 5). Time to response was short, with a mean time to response of 5.1 days (SD, 2.0). When used as a second-line agent, duration of response was also short relative to other agents described in this study (mean duration of response, 6.1 months; SD, 11.0). A high percentage of patients (46%) experienced adverse events with dexamethasone, most commonly anxiety, headache, and sleep disturbance (Table 6).

Mycophenolate was used as subsequent therapy in 10 patients (Table 5). Eight (80%) of these individuals received this as a second-line option (Table 5). The mean time to response for all patients receiving mycophenolate was 32.6 days (SD, 13.5) and mean duration of response was 13.2 months (SD, 12.5). Two patients received adjunct steroids with a mean duration of wean of 33 days. Patients receiving adjunct steroids once again had a shorter time to response (mean time to response, 28 days vs. 38.7 days, respectively). However, the use of adjunct steroids did not affect the overall duration of response compared to those not requiring adjunct steroids (mean duration of response, 13 months; SD, 9.9 vs. 13.3 months; SD, 16.3, respectively). There were no adverse events reported with mycophenolate use in this study.

Cyclophosphamide was used as a second-line therapy in two patients (Table 5). A response of 4 months was reported in one of two patients treated with the drug but was discontinued due to intolerable nausea. Finally, danazol was used as a second-line therapy in one patient with adjunct prednisone (Table 5). The dosage of danazol was 200 mg daily, which resulted in a complete response after 79 days that was maintained for 56 months. There were no reported side effects associated with danazol in this study.

4 | DISCUSSION

This multicenter retrospective observational study of the treatment of ITP in Australia aimed to describe the use, effectiveness, and tolerability of ITP treatments in use in Australia. Corticosteroids remain the mainstay of treatment, but their long-term use was associated with significant side effects, primarily metabolic, that frequently result in their discontinuation. Furthermore, failure of first-line treatment is common, with patients in the study population using on average 2.04 lines of treatment (SD, 1.28) before experiencing sustained response to treatment.

This study included multiple Australian centers. Because the study population consisted of patients hospitalized with ITP or under the care of a specialist hematologist, it is possible that the study population contained a greater proportion of severe and/or chronic ITP. Demographically, the study population was consistent

with descriptions in existing literature, with a mean age at diagnosis of 48.85 and a 58% female predominance.^{6,12} Despite collecting data from community hospitals and tertiary metropolitan centers across three states, there was no statistically significant regional variation in patient demographics, platelet count, bleeding, or duration of hospitalization.

The retrospective design of the study meant that data collection was limited to information that was universally available in medical records across all participating centers. Demographic information regarding ethnicity is not routinely collected for public hospital patients in Australia, which may have been useful in identifying genetic or sociocultural factors influencing the effectiveness or tolerability of the treatments studied. Detailed assessment of patient outcomes was also limited by the information available in medical records, such that some relevant information such as bleeding requiring transfusion of blood or platelets could not be collected for all patients.

Across all centers, initial treatment was in keeping with contemporary guideline-recommended therapy,^{2,8,13} with most patients receiving either prednisone alone or in combination with IVIG. There was notable variability in the duration of prednisone weans across centers, with average duration ranging from 53 to 432 days; however, the details of prednisone weaning dosage were not captured in this study.

Although this study was not designed or powered to demonstrate superiority of one second-line agent over another, we observed significant differences in effectiveness and tolerability between these agents with a signal favoring rituximab and thrombopoietin agonists. Because of the observational study design, subgroup sample sizes for agents used in subsequent lines of therapy were relatively small, with large variance for assessing rates and duration of responses. Furthermore, the use of treatment data from a fixed study period (2013–2020) may have influenced study results regarding duration of response, with treatments accessed earlier in the study period having potentially longer durations of observed follow-up. Due to the relatively small sample sizes of subgroups using each individual agent, statistical modeling and subgroup analysis could not be performed on these data. Future research can build on the results of this study to perform direct comparisons of second-line agents.

In keeping with the understanding of ITP as a heterogeneous disease, it is unlikely that there is a single agent that is best used as a second- or subsequent-line agent in all patients, so a role for the multiple immunosuppressive and immune-modulating agents in use as subsequent therapies is likely to persist despite improving access to TPO-As and rituximab in the Australian setting.

A review of existing literature does not identify a link between the presence of specific antiplatelet antibodies in ITP and response to specific second-line therapies.^{3,14} In practice, prescribing of second- and subsequent-line agents continues to be guided by prescriber experience and drug availability within the health care system. Although our data regarding effectiveness and tolerability of second-line agents suggests favorable profiles for rituximab and thrombopoietin agonists relative to other agents,

these were not the most used therapies and were most commonly employed after multiple previous agents were discontinued either due to loss of response or side effects, including in relapsed ITP following splenectomy. This practice is likely reflective of limitations to prescription of these agents placed on practitioners by hospital and national governing bodies. In Australia, thrombopoietin agonists are eligible for PBS funding only for the treatment of chronic ITP following splenectomy.¹³ While rituximab was not reimbursed by the PBS as a treatment for ITP during the study period, decreases in the cost of the drug during the study period could be expected to improve access for Australian patients.¹³

Current international guidelines including the 2019 update to the ASH guidelines, as well as a recently published Australasian consensus guideline recommend the use of rituximab and TPO-As as splenectomy-sparing agents following the failure of first-line treatment.^{2,6,13} In comparison to previous studies investigating the effectiveness and tolerability of these agents, our data show similar rates of response/complete response for these agents^{15–17} with a lower rate of side effects from rituximab than has previously been reported elsewhere.¹⁷

Overall, our data suggest that effective second- and subsequent-line therapies exist for ITP; however, current limitations to access to these agents in the Australian context, as well as a lack of robust head-to-head comparisons of multiple agents, mean that prescribing patterns are largely driven by the experience of individual prescribers.

AUTHOR CONTRIBUTIONS

AR: study design, ethics application, design of data collection tool, data collection—Lismore Base Hospital, Concord and Repatriation Hospital. CC: site-specific ethics and data collection—Royal North Shore Hospital, literature review. FA: site-specific ethics and data collection—Westmead Hospital. HH: data collection—Westmead Hospital. RKB: biostatistical support. VC: coinvestigator, site supervisor—Concord and Repatriation Hospital. HC: coinvestigator, site supervisor—Blacktown and Mount Druitt Hospital. JC: coinvestigator, site supervisor—Westmead Hospital. ED: site-specific ethics and data collection—Nepean Hospital. CWTan: coinvestigator, site supervisor—The Royal Adelaide Hospital. YT: coinvestigator, site supervisor—Nepean Hospital. AV: data collection—The Royal Adelaide Hospital. CMW: coinvestigator, site supervisor—The Royal North Shore Hospital. RB: coinvestigator, site supervisor, and data collection—The Princess Alexandra Hospital. DJRabbolini: principal investigator, study design, site supervisor—Lismore Base Hospital. All investigators listed above contributed to preparation of the draft and final manuscript.

RELATIONSHIP DISCLOSURE

The authors report no conflicts of interest in this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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