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REVIEW ARTICLE

Corticosteroid overuse in adults with immune thrombocytopenia: Cause for concern

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Abstract

Corticosteroids remain a crucial component of first-line therapy for immune thrombocytopenia (ITP) due to low cost, high initial response rates, and acceptable short-term tolerability. However, extended and recurrent use of corticosteroids is associated with substantial toxicity. Survey studies indicate that >95% of patients with ITP treated with corticosteroids report adverse effects, more than one-third of whom require reduction or discontinuation of treatment. In light of the heavy treatment burden of prolonged corticosteroid exposure, clinical practice guidelines recommend limiting corticosteroid treatment to no more than 6 weeks in adults with ITP receiving initial therapy. For patients who require subsequent therapy, clinical practice guidelines recommend treatments more suitable for long-term disease control such as thrombopoietin receptor agonists, rituximab, other immune-modulating medications, or splenectomy, rather than repeated courses of corticosteroids. Despite these recommendations, real-world evidence suggests that corticosteroids remain the most frequently used treatment for adults with ITP, not only in the first line, but also in the second and third line. In this review, we summarize evidence on the efficacy, safety, and tolerability of corticosteroids; discuss the problem of overuse; and suggest strategies for curtailing the excessive use of corticosteroids in adults with ITP.

KEYWORDS
corticosteroids, review, safety, thrombocytopenia, thrombopoietin receptors

Essentials

- Corticosteroids are a mainstay of immune thrombocytopenia (ITP) treatment, but are associated with substantial toxicity.
- ITP guidelines therefore recommend against prolonged or repeated courses of steroids.
- Nevertheless, overuse of steroids remains common.
- We propose strategies for curtailing excessive steroid use in patients with ITP.

1 | INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune disease associated with impairment of platelet production and immune-mediated platelet destruction, resulting in low platelet counts.[1-3] Patients present with a variable bleeding tendency and may also experience fatigue or impaired health-related quality of life (HRQoL).[4-6] Estimates of the incidence of acute ITP in adults range from 1.1 to 6.6 cases per 100 000 per year.[7-9] Recent epidemiologic studies from the United Kingdom and Taiwan show an increasing incidence of ITP after age 50, confirming that the disease has a rising prevalence in older adults,[8,10,11] who are more susceptible to corticosteroid toxicity.[12] ITP may be classified as primary (not attributable to a recognized predisposing condition), or secondary when it occurs in association with a recognized predisposing condition, as well as by chronicity (eg, newly diagnosed ITP [<3 months], persistent ITP [3–12 months], and chronic ITP [>12 months]).[13,14]

In patients with newly diagnosed ITP, guidelines recommend use of corticosteroids, supplemented as needed with intravenous immunoglobulin (IVIg) or anti-D, for first-line treatment. Patients who do not respond to or relapse after first-line treatment is tapered require second-line therapy. Options include thrombopoietin receptor agonists (TPO-RAs; eg, avatrombopag, eltrombopag, and romiplostim), rituximab, fostamatinib, other immune-modulating medications, and splenectomy.[2,3] Given the potential risks of surgical intervention, and reduced rates of durable response in patients aged >40 years, patients and clinicians increasingly opt for medical therapy over splenectomy in the second line.[2,3,15-17]

Although corticosteroids are a mainstay of initial therapy in ITP, current recommendations advise against their use for >6 weeks to minimize cumulative toxicity.[2] Standard corticosteroid regimens include high-dose dexamethasone administered at 40 mg daily for 4 days, often given for 1 to 2 cycles, or prednisone/prednisolone at a dose of 0.5 to 2 mg/kg daily for several weeks.[2] Guidelines recommend monitoring patients for potential corticosteroid-related adverse events, such as mood disturbances, gastric irritation, hyperglycemia, weight gain, insomnia, and myopathy. In patents receiving long-term corticosteroid therapy, adverse events may include osteoporosis and glaucoma.[2] With multiple available corticosteroid-sparing treatment options for ITP, it is important to reexamine the potential serious adverse events associated with use of glucocorticoids in ITP and to evaluate the potential risk-benefit balance of long-term corticosteroid therapy compared with other therapies.

2 | CORTICOSTEROID EFFICACY

Based on seven randomized controlled trials published over the past 10 years (Table 1),[18-24] the range of initial platelet response rates (platelet count ≥30 × 10^9/L over a period of at least 7 days) was 10% to 100% with high-dose dexamethasone, 17% to 69.1% with prednisone, and 43.3% to 100% with prednisolone. Overall, initial response rates with corticosteroids across trials were ≈70%.

Sustained platelet response (platelet count ≥30 × 10^9/L) after 6 to 48 months ranged from 16.6% to 40% with high-dose dexamethasone, 23.5% to 41.2% with prednisone, and 36% to 40% with prednisolone. The rate of sustained complete response (platelet count ≥100 × 10^9/L) after ≥6 months of follow-up ranged from 27.4% to 73.3% with high-dose dexamethasone, whereas single studies reported sustained complete response rates of 17.5% with prednisone and 6.6% with prednisolone.[18,20-24] Overall, sustained platelet response rates with corticosteroids at ≥6 months of follow-up are ≈30% across trials.

Other evidence evaluating the efficacy of corticosteroids, including meta-analyses and retrospective analyses, are presented in Table 2.[25-28] A meta-analysis identified improved short-term response at day 14 with high-dose dexamethasone versus prednisone in terms of both overall response (risk ratio, 1.22; 95% confidence interval [CI], 1.00-1.49) and complete response (risk ratio, 1.67; 95% CI, 1.02-2.72). However, rates of long-term complete response at month 6 with high-dose dexamethasone versus prednisone were not significantly different (risk ratio, 1.16; 95% CI, 0.79-1.71).[26] A network meta-analysis examined corticosteroids as part of combination therapy. Response rates as evaluated by surface under the cumulative ranking curve were highest when corticosteroids were used in combination with TPO-RAs (97.1% for sustained response and 97.1% [with prednisolone] and 82.4% [with dexamethasone] for short-term response). High rates of response were also observed in patients receiving corticosteroids with rituximab (81.3% for sustained response and 74.7% for short-term response).[25]

3 | SAFETY AND TOLERABILITY OF CORTICOSTEROIDS

Corticosteroid therapy is associated with serious adverse events, including acute effects of mood disturbances, gastric irritation, hyperglycemia, weight gain, insomnia, and myopathy, as well as adverse events associated with longer-term use, including osteoporosis and glaucoma.[2,3] Glucocorticoid therapy increases the risk of bone fractures by 75% within 3 months of initiation and induces measurable losses in bone mineral density within 6 months of starting therapy. Monitoring for diabetes mellitus, cataracts, glaucoma, and cardiovascular health, as well as screening for infectious diseases, is recommended for all patients receiving long-term corticosteroid therapy (eg, a treatment course >6 weeks).[2,29,30]

In our review of studies published since 2009 evaluating corticosteroid toxicity in adult patients with ITP, we identified a total of 16 studies including 2 meta-analyses, 7 randomized trials, a retrospective analysis, and 4 surveys (Table 3).[18-26,28,31-35]

- *Meta-analyses.* A network meta-analysis identified an overall adverse event rate with dexamethasone monotherapy of 4.1% (22/531) across adult patients with newly diagnosed ITP over 3 to 6 months of follow-up. Of the 22 adverse events in dexamethasone-treated patients, all were rated as severe adverse

TABLE 1 Response rates with corticosteroids in ITP

Study	Design	Efficacy	HD-DEX, %	HD-DEX-M, %	3×HD-DEX, %	PDN	PSL	Other	*P* value
Wei 2016[18]	A prospective multicenter trial of HD-DEX (40 mg daily for 4 d; n = 95) vs PDN (1.0 mg/kg daily for 4 wk, then tapered; n = 97) in adults with ITP followed for up to 36 m	PR	82.1			69.1			.04
		CR	50.5			26.8			.001
		SR (PR)[a]	40.0			41.2			.88
		SR (CR)[a]	27.4			17.5%			.12
		Median (range) TTR in days	3 (1-9)			6 (2-24)			<.001
Sun 2016[19]	A retrospective study of ITP in pregnancy in 195 women across 235 pregnancies, including 51 patients receiving corticosteroids (mean dose 0.65 mg/kg/d PDN for a median of 10 d) initially and 47 patients receiving IVIg (1 g/kg)	PR[b]				39[c]		38 (IVIg)	.85
		Blood product used (%)				5.9[c]		19.2 (IVIg)	.05
Din 2015[20]	Single-center randomized study of HD-DXM (40 mg daily for 4 d; including groups receiving maintenance DEX 0.035 mg/kg/d [HD-DXM-M; n = 30] and without maintenance [HD-DXM-nM; n = 31]) versus PDN (1 mg/kg/d) (n = 29) followed for a median of 16 m (range: 12-21 m). Long-term outcomes reported at month 12	PR[d]	20	27		17			<.05
		SR (PR)[d]	40.0	63.4		23.5			<.05
Nakazaki 2012[21]	Prospective randomized study of previously untreated adult ITP with: • PSL (0.5–1 mg/kg daily PSL for 2-4 wk followed by taper; n = 8) • HD-DXM (DEX 40 mg daily for 4 d; n = 12) • 3×HD-DXM (up to 3 courses of 1×HD-DXM over the course of 21 mo; n = 5) The median follow-up was 32.2 mo (range, 1.3-102.6 mo)	PR[b]	75		100		100		0.17 (PSL vs HD-DEX) 0.13 (PSL vs 3×HD-DEX)
		CR	33		80		75		NR
		Mean (SD) TTR in days	5.0 (2.0)		11.8 (8.0)		11.4 (12.3)		0.26

(Continues

TABLE 1 (Continued)

Study	Design	Efficacy	HD-DEX, %	HD-DEX-M, %	3×HD-DEX, %	PDN	PSL	Other	*P* value
Mashhadi 2012[22]	Randomized prospective study of HD-DEX 40 mg/d for 4 d (n = 30) versus conventional PSL 1 mg/kg/d tapered over 6 wk (n = 30) therapy in adults with newly diagnosed symptomatic ITP in Iran followed for 12-48 mo	PR[e]	10				43.3		.02
		CR[e]	90				36.7		.02
		SR (PR)[f]	16.6				40		<.0001
		SR (CR)[f]	73.3				6.6		<.0001
Bae 2010[23]	A prospective randomized multicenter trial of conventional-dose PSL (1 mg/kg/d; n = 60) versus HD-DEX (40 mg/d for 4 d; n = 57) in patients with newly diagnosed ITP in Korea followed for at least 6 mo	PR	68.2				81.2		NR
		SR (PR)[g]	25.0				36.0		.33
Praituan 2009[24]	Randomized trial of short-course DEX before PSL (10 mg every 6 h for 4 d followed by PSL 30 mg daily; n = 18) versus high-dose PSL (PSL 60 mg daily; n = 18) in adults with primary ITP in Thailand with up to 6 mo of follow-up	PR	94.4				61.1		.04
		R	88.8				33.3		.001

Note: PR defined by platelet count ≥30 × 10^9/μL. R defined by platelet count ≥50 × 10^9/μL. CR defined by platelet count ≥100 × 10^9/μL. Sustained response is defined by varying platelet cutpoints (PR, R, or CR), as indicated.

Abbreviations: CR, complete response; DEX, dexamethasone; HD-DEX, high-dose dexamethasone; ITP, immune thrombocytopenia; ITT, intent to treat; IVIg, intravenous immunoglobulin; NR, not reported; PDN, prednisone; PR, platelet response; PSL, prednisolone; R, response; SD, standard deviation; SR, sustained response; TTR, time to response.

[a]Additional criteria include having bleeding symptoms and/or no requirement for additional ITP-modifying treatment in the 6 mo (consecutively) following initial response.

[b]Required PR plus an increase in platelet levels to at least twice baseline levels.

[c]Includes 51 patients treated with corticosteroids, 46 of whom received PDN, 4 of whom received DEX, and 1 of whom received both PDN and DEX.

[d]Required PR plus an increase in platelet levels to at least twice baseline levels and absence of bleeding.

[e]At 1 wk.

[f]At 1 y.

[g]In the ITT population.

TABLE 2 Other evidence of the safety and efficacy of corticosteroids in ITP

Study	Design	Efficacy Considerations
Arai 2018[25]	Network meta-analysis of randomized controlled trials evaluating treatments for newly diagnosed ITP evaluating sustained response rates, overall response rates, safety, and tolerability across 21 randomized controlled trials (n = 1898)	Based on SUCRA for specific treatment combinations in inducing sustained response and overall response. In terms of sustained response over 3 to 6 mo of follow-up, treatments and SUCRA scores were rhTPO +DEX (97.1%), RTX +DEX (81.3%), and RTX +DEX + PSL (81.1%). In terms of overall short-term response, SUCRA scores were rhTPO +PSL (97.1%), rhTPO +DEX (82.4%), and RTX +DEX + PSL (74.7%)
Mithoowani 2016[26]	Meta-analysis of a pooled group of 529 patients across 5 trials of short-course HD-DEX (n = 280) versus long-term PDN (n = 249) in patients with previously untreated ITP	Overall response rates at day 14 (risk ratio: 1.22; 95% CI, 1.00-1.49) and complete response rates at day 14 (risk ratio: 1.67; 95% CI, 1.02–2.72) were significantly higher with short-course HD-DEX, but there were no significant differences in complete response rates at month 6 (risk ratio, 1.16; 95% CI, 0.79-1.71)
Michel 2011[27]	Retrospective analysis of two 6-mo phase 3 trials comparing corticosteroid use in patients randomized to romiplostim (n = 83) versus placebo (n = 42) in adults with primary ITP	Use of the TPO receptor agonist romiplostim decreased use of corticosteroids by 30% during the first 4 wk of therapy. Corticosteroid use per 100 wk of romiplostim use was 15.0 wk versus 23.4 to 30.5 wk in patients receiving placebo. A significant 13% ($P = .0003$) decrease in the odds of corticosteroid use was observed for every 24 wk of romiplostim treatment received
Frederiksen 2014[28]	A retrospective study of 221 patients in Denmark with primary ITP observed over a median of 197.3 mo (IQR, 84.5-283.2 mo)	At diagnosis, 69% of patients were treated with corticosteroids; 6% of patients received corticosteroids with other medications, such as IVIg; and 25% of patients were not treated. Cumulative mortality rates were higher in patients with ITP versus the general population at year 5 (22% vs 12%), 10 (34% vs 23%), and 20 (49% vs 42%). HRs indicate higher rates of cardiovascular disease (HR, 1.5), infection (HR, 2.4), bleeding (HR, 6.2), and hematological cancer (HR, 5.7) in patients with ITP versus the general population. Authors noted that use of immunosuppressive therapies, including corticosteroids, may have contributed to elevated levels of malignancy in patients with ITP

Abbreviations: CI, confidence interval; DEX, dexamethasone; HD-DEX, high-dose dexamethasone; HR, hazard ratio; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; PDN, prednisone; PSL, prednisolone; rhTPO, recombinant human thrombopoietin receptor agonist; RTX, rituximab; SUCRA, surface under the cumulative ranking curve; TPO, thrombopoietin.

events (ie, Common Terminology Criteria for Adverse Events [CTCAE] grade ≥3). The most common severe adverse events included hyperglycemia, hypertension, and gastrointestinal distress.[25] In a pooled group of 529 patients, adverse events included gastrointestinal toxicities (6%), hyperglycemia (6%), weight gain (5%), insomnia/fatigue (3%), and hypertension (3%).[26]

- *Randomized trials*. Across seven randomized trials, adverse events were reported over variable periods of time, ranging from 1 week to >8 years of follow-up, with all but one trial[31] reporting at least 6 months of follow-up data.[18,20-24,31] Wei et al. identified adverse events occurring in more than half of patients treated with corticosteroids (56.3%;108/192) for up to 36 months of follow-up.[18] Notably, a higher percentage of adverse events related to high-dose dexamethasone use were observed in patients aged ≥60 years versus younger patients, including higher rates of insomnia (16.7% vs 8.4%), mood disorders (11.1% vs 7.4%), hypertension (11.1% vs 4.2%), and hyperglycemia (5.6% vs 4.2%). In patients receiving prednisone, higher rates of adverse events were also observed in patients aged ≥60 years, including weight gain (15.0% vs 10.3%), hypertension (15.0% vs 8.2%), and hyperglycemia (15.0% vs 6.2%).[18] Not all studies reported adverse events by grade. However, Bae et al. reported five cases (8.8%) of grade 3 hyperglycemia with high-dose dexamethasone in 57 patients; Mashhadi et al. identified three cases (5.0%) of grade 3 gastrointestinal distress among 60 patients treated with either high-dose dexamethasone or conventional prednisolone; and Nakazaki et al. reported two cases (25.0%) of grade 3 or 4 adverse events in 8 patients randomized to short-course prednisolone.[21-23] In a study by Din et al,[20] 10 adverse events were identified in 61 patients randomized to pulsed dexamethasone, which resulted in treatment discontinuation in 4 patients. Similarly, a small study by Praituan et al. reported 8 adverse events in 18 patients treated with the combination of short-course dexamethasone followed by prednisolone versus 6 adverse events in 18 patients randomized to prednisolone alone. Although severity was not assessed, there were no discontinuations due to steroid-related adverse events.[24] One study evaluating corticosteroid use for 1 week following splenectomy identified 11 adverse events in 50 patients. Adverse events did not result in lack of tolerability and were not serious enough to result in treatment discontinuation.[31]

TABLE 3 Safety of corticosteroids in ITP

Study	Design	Group	Adverse Events
Arai 2018[25]	Network meta-analysis of randomized controlled trials evaluating treatments for newly diagnosed ITP evaluating sustained response rates, overall response rates, safety, and tolerability across 21 randomized controlled trials (n = 1898)	Severe AEs (CTCAE grade 3 or higher) in corticosteroid-treated patients	Rate of severe AEs in DEX-treated patients: 4.1% (22/531)
Wei 2016[18]	A prospective multicenter trial of HD-DEX (40 mg daily for 4 d; n = 95) vs PDN (1.0 mg/kg daily for 4 wk, then tapered; n = 97) in adults with ITP followed for up to 36 mo	HD-DEX arm (total population)	AEs in the HD-DXM arm (percentage in the total population): Insomnia (8.4%), mood disorders (7.4%), hypertension (4.2%), and hyperglycemia (4.2%)
		HD-DEX arm (patients aged >60 years)	Insomnia (16.7%), mood disorders (11.1%), hypertension (11.1%), and hyperglycemia (5.6%)
		PDN arm (total population)	Cushingoid appearance (13.4%), weight gain (10.3%), hypertension (8.2%), hyperglycemia (6.2%)
		PDN arm (patients aged >60 y)	Cushingoid appearance (10%), weight gain (15%), hypertension (15%), hyperglycemia (15%)
Mithoowani 2016[26]	Meta-analysis of a pooled group of 529 patients across 5 trials of short-course HD-DEX (n = 280) versus long-term PDN (n = 249) in patients with previously untreated ITP	All patients	All patients: Gastrointestinal toxicities (6%), hyperglycemia (6%), weight gain (5%), insomnia/fatigue (3%), and hypertension (3%)
		Short-course HD-DEX	Gastrointestinal toxicities (5%), hyperglycemia (5%), insomnia/fatigue (3%), and anxiety/mood disorder (3%)
		Long-term PDN	Weight gain (9%), gastrointestinal toxicities (8%), hyperglycemia (6%), Cushingoid appearance (5%)
Sun 2016[19]	A retrospective study of ITP in pregnancy in 195 women across 235 pregnancies, including 51 patients receiving corticosteroids (mean dose 0.65 mg/kg/d PDN for a median of 10 d) initially and 47 patients receiving IVIg (1 g/kg)	AEs in 67 pregnant women treated with corticosteroids	13.4% (9/67) AEs included hyperglycemia requiring treatment (9%), hyperglycemia with neonatal hypoglycemia (2%), infection (2%), and insomnia/jitteriness (2%)
Din 2015[20]	Single-center randomized study of HD-DXM (40 mg daily for 4 d; including groups receiving maintenance DEX 0.035 mg/kg/d [HD-DEX-M; n = 30] and without maintenance [HD-DEX-nM; n = 31]) versus PDN 1 mg/kg/d (n = 29) followed for a median of 16 mo (range, 12-21 mo)	AEs occurring with HD-DEX induction therapy in both HD-DEX-M and HD-DEX-nM patients (n = 61)	16.4% (10/61) AEs included anxiety (n = 2), gastric distress (n = 2), and steroid-induced diabetes (n = 2). AEs that led to trial discontinuation included severe vomiting (n = 3) and transitory hypertension (n = 1)
Suvajdzic 2014[32]	Survey of HRQoL of adult patients with chronic ITP in Serbia (n = 111)	Percentage of patients with self-reported AEs associated with corticosteroid treatment	96.5%

(Continues)

TABLE 3 (Continued)

Study	Design	Group	Adverse Events
Nakazaki 2012[21]	Prospective randomized study of previously untreated adult ITP with: • PSL (0.5–1 mg/kg daily PSL for 2 to 4 wk followed by taper; n = 8) • 1×HD-DEX (DEX 40 mg daily for 4 d; n = 12) • 3×HD-DEX (up to 3 courses of 1×HD-DEX over the course of 21 mo; n = 5) The median follow-up was 32.2 mo (range 1.3-102.6 mo)	PSL	75% (6/8) AEs included hypertension (2/8), hyperglycemia (2/8), hyperlipidemia (1/8), and insomnia (1/8). Grade 3/4 AEs included 1 case of hypertension and 1 case of atrial flutter
		1×HD-DEX	42% (5/12) AEs included insomnia (2/12), hyperglycemia (1/12), gastrointestinal pain (1/12), and flushing (1/12)
		3×HD-DEX	40% (2/5) AEs included hyperglycemia (1/5) and insomnia (1/5)
Mashhadi 2012[22]	Randomized prospective study of HD-DEX 40 mg/d for 4 d (n = 30) versus conventional PSL 1 mg/kg/d tapered over 6 wk (n = 30) therapy in adults with newly diagnosed symptomatic ITP in Iran followed for 1248 mo	HD-DEX	AEs included weight gain (17.3%), glucose intolerance (3.3%), hypertension (3.3%), and gastrointestinal distress (6.6%)
		Conventional PSL	AEs included weight gain (43.3%), glucose intolerance (16.5%), hypertension (10%), and gastrointestinal distress (23.3%)
Brown 2012[33]	Survey of patients with chronic ITP in 589 patients who are members of a US-based support group	Percentage of patients receiving corticosteroids experiencing AEs	98%
		Percentage of patients highly bothered by steroid-related AEs	53.1%
		Percentage of patients requiring dose reduction or discontinuation of treatment to reduce AE severity	37.8%
Newton 2011[34]	A survey study of 585/1871 members of the UK ITP Support association and 68/93 patients enrolled in the Oklahoma ITP Registry evaluating fatigue, daytime sleepiness, and orthostatic symptoms associated with ITP	Percentage of patients receiving steroids experiencing fatigue	50%
Bilgir 2011[31]	A study of conventional-dose steroid treatment (1 mg/kg; n = 20) versus high-dose steroid (30 mg/kg methylprednisolone; n = 30) treatment prior to splenectomy in Turkey; patients were followed for 1 wk after their procedure	Percentage of patients experiencing AEs in the high-dose steroid arm	20% (6/30) AEs included infection (3.3%), steroid-induced diabetes mellitus (3.3%), gastrointestinal symptoms (10%), and hypertension (3.3%)
		Percentage of patients experiencing AEs in the conventional-dose steroid arm	25% (5/20) AEs included steroid-induced diabetes mellitus (5%), gastrointestinal symptoms (10%), hypertension (5%), and Cushingoid appearance (5%)
Bae 2010[23]	A prospective randomized multicenter trial of conventional-dose PSL (1 mg/kg/d; n = 60) versus HD-DEX (40 mg/d for 4 d; n = 57) in patients with newly diagnosed ITP in Korea followed for ≥6 mo	Percentage experiencing AEs with conventional-dose PSL resulting in treatment discontinuation	5% (3/60) Pneumonia (n = 1), hyperglycemia (n = 1), and myalgia (n = 1)
		Percentage experiencing AEs with HD-DEX resulting in treatment discontinuation	10.5% (6/57) Grade 3 hyperglycemia (n = 5), other (n = 1)

(Continues)

TABLE 3 (Continued)

Study	Design	Group	Adverse Events
Praituan 2009[24]	Randomized trial of short-course DEX prior to PSL (10 mg every 6 h for 4 d followed by PSL 30 mg daily; n = 18) versus high-dose PSL (PSL 60 mg daily; n = 18) in adults with primary ITP in Thailand with up to 6 mo of follow-up	Percentage of patients experiencing AEs in the DEX/PSL group	44% (8/18) Hyperglycemia (n = 1), dyspepsia (n = 3), acne (n = 4)
		Percentage of patients experiencing AEs in the high-dose PSL group	33% (6/18) Dyspepsia (n = 4), acne (n = 2)
Guidry 2009[35]	Survey of hematologists (n = 83, of whom 71% responded) and patients (n = 80, of whom 80% responded) regarding side effects of corticosteroid therapy through the Oklahoma ITP Registry	AEs reported by patients	• Moon face, bloating, or swelling (43%) • Weight gain/increased appetite (41%) • Hair loss (13%) • Acne (11%) • Stretch marks (10%) • Insomnia, restlessness, or trouble sleeping (28%) • Anxiety and/or nervousness (24%) • Depression and/or stress (23%) • Anger and/or irritability (21%) • Generalized weakness or fatigue (22%) • Muscle weakness (16%) • Body pain (21%) • Hot flush/sweating (17%) • Visual problems (11%)
		AEs reported by hematologists	• Moon face, bloating, or swelling (27%) • Weight gain/increased appetite (31%) • Hair loss (3%) • Acne (2%) • Stretch marks (8%) • Insomnia, restlessness, or trouble sleeping (17%) • Anxiety and/or nervousness (9%) • Depression and/or stress (4%) • Anger and/or irritability (9%) • Generalized weakness or fatigue (7%) • Muscle weakness (7%) • Body pain (0%) • Hot flush/sweating (2%) • Visual problems (2%)

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DEX, dexamethasone; HD-DEX, high-dose dexamethasone; HD-DEX-M, high-dose dexamethasone with maintenance; HD-DEX-nM, high-dose dexamethasone without maintenance; HRQoL, health-related quality of life; IQR, interquartile range; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; PDN, prednisone; PSL, prednisolone.

- *Retrospective analyses*. In a retrospective analysis, use of steroids was evaluated in pregnant women with ITP. Adverse events associated with corticosteroids included hyperglycemia requiring treatment (9%) and neonatal hypoglycemia (2%).[19] A long-term registry study conducted over 20 years implicated immunosuppressive therapies, including steroids, as a potential factor in higher rates of malignancy and reduced life expectancy in ITP. Although no increase in the risk of developing solid tumors in patients with ITP versus matched patients in the general population comparison group was detected, at year 20, the risk of hematologic malignancies was elevated significantly in patients with ITP (2.8% vs 1.0%; crude hazard ratio, 3.7 [95% CI, 1.6-8.6], adjusted hazard ratio, 5.7 [95% CI, 2.1-15.7]).[28]
- *Surveys*. Four survey studies identified a high rate of patient-reported and physician-reported adverse events with corticosteroids.[32-35] Among 111 patients with ITP in Serbia treated with corticosteroids, the vast majority (96.5%) reported corticosteroid-related adverse events.[32] Similarly, a survey of 589 patients with ITP found that 98% of patients receiving corticosteroids experienced adverse events, with more than one-third of patients

(37.8%) requiring dose reduction or discontinuation of treatment as a result. Among all classes of medications used in ITP, survey participants rated corticosteroids as significantly more bothersome than other therapeutic alternatives ($P < .05$).[33] In another survey of 585 members of the UK ITP Support Association and 68 members of the Oklahoma ITP Registry, corticosteroid use was associated with increased fatigue on a univariate analysis of HRQoL.[34] Physicians may underestimate the impact of corticosteroid toxicity on their patients. In a survey of patients with ITP and hematologists, patients reported a significantly ($P <.05$) greater frequency of corticosteroid-related side effects on 13 of 18 categories of adverse events. The most common reported adverse events were moon face, bloating, and swelling; weight gain/increased appetite; and insomnia, restlessness, or trouble sleeping.[35]

Among the randomized trials that reported adverse events by grade, the incidence of serious adverse events (grade ≥3) ranged from 5.0% to 25.0%.[21-23] The median adverse event rate among the 19 studies conducted over the past 10 years that reported adverse events was 33% (range, 3.2%-98%). In survey studies, >95% of patients reported corticosteroid-associated adverse events, suggesting that clinical trials and observational studies may underestimate the true patient burden.[32,33] In fact, more than half of adverse events (53.1%) were rated by patients as "very bothersome," and more than one-third (37.8%) were reported as leading to reduction or discontinuation of corticosteroid therapy.[33]

4 | GUIDELINE RECOMMENDATIONS

Current guidelines and guidance documents for ITP include the 2019 American Society of Hematology (ASH) guideline[2] and the updated international consensus report.[3] These documents are supplemented by Chinese and Brazilian guidance published in 2018.[36,37]

Updated ASH guidelines recommend first-line treatment with corticosteroids in asymptomatic adult patients and patients with minor mucocutaneous bleeding with platelet levels $<30 \times 10^9$/L. The ASH guidelines also recommend limiting the duration of initial corticosteroid treatment in adults with newly diagnosed ITP to short-course therapy (ie, ≤6 weeks), citing the unfavorable risk-benefit balance of prolonged corticosteroid use in this population.[2]

Consistent with this, the international consensus report recommends use of corticosteroids for a limited time in adults with newly diagnosed ITP and notes the importance of monitoring HRQoL in patients receiving long-term steroid therapy.[3] Chinese guidelines published in 2018 also recommend a short course of therapy of <4 weeks followed by a rapid taper for adult patients with ITP who do not respond to initial therapy and generally favor pulsed high-dose dexamethasone over long-term corticosteroid therapy.[36] Brazilian guidance also mentions a faster onset of effect with high-dose corticosteroids and pulsed dexamethasone. However, it does not make specific recommendations regarding limiting treatment-related adverse events or the preferred duration of initial corticosteroid therapy.[37]

5 | OVERUSE

Overuse of corticosteroids in newly diagnosed adult ITP is well documented in the literature and is inconsistent with current clinical practice guidelines. In a real-world analysis of ITP treatment using administrative claims data, corticosteroids were used in >90% of patients and as the initial line of therapy in 85% to 88% of cases. Corticosteroids continued to be the most common treatment strategy in second- and third-line therapy, having been administered in >80% of all cases. Treatments other than corticosteroids accounted for 7% to 8% of all treatments administered across lines of therapy (including IVIg, splenectomy, rituximab, and TPO-RAs).[38] A Spanish registry study reported that 40.6% of patients with primary ITP received corticosteroid monotherapy and 32.8% received corticosteroid therapy combined with IVIg.[39] At variance with clinical practice guidelines,[2] 59.5% of these patients had a treatment duration of >6 weeks.[39] A nationwide health insurance review conducted in Korea reported first-line corticosteroid monotherapy in 42% of patients treated for ITP and corticosteroids plus IVIg in 19%.[40] After 3 months, 75% of adults were still on treatment, 63% of whom were receiving corticosteroid monotherapy. Even at 48 months, among those who remained on ITP therapy, more than half were on corticosteroids. Given the inconsistency of these practice patterns with current guidelines and the well-documented burden to patients of extended corticosteroid exposure,[32-34] there is a need to curtail the overuse of corticosteroids and expand use of other treatment options that are more suitable for later lines of treatment.

6 | ALTERNATIVES TO CORTICOSTEROIDS

In addition to corticosteroids, initial treatment options listed by current treatment guidelines include IVIg and anti-D.[2,3] Subsequent treatment options that are supported by robust evidence include TPO-RAs, rituximab, fostamatinib, and splenectomy. TPO-RAs, which include avatrombopag, eltrombopag, and romiplostim, have been studied in multiple clinical trials in ITP.[2,3] In a phase 3 trial, among 32 patients randomized to avatrombopag therapy, platelet response (platelet count $\geq 50 \times 10^9$/L) occurred in 66% of patients at day 8 and was durable, with patients maintaining a platelet response for a median of 12.4 weeks during the 24-week trial. Treatment was generally well tolerated, with the most common adverse event being headache.[41] Similarly, in a phase 3 trial of eltrombopag in adults with ITP, response (platelet count $\geq 50 \times 10^9$/L) was observed at day 8 in 44% of 30 patients randomized to eltrombopag 50 mg daily and 62% of 29 patients randomized to eltrombopag 75 mg daily. Mild to moderate headache was the most common adverse event.[42] Attainment of response (platelet counts $\geq 50 \times 10^9$/L) occurred in 25% of 83 patients randomized to romiplostim within 1 week of initiating

therapy at 1 μg/kg. Headache, fatigue, and arthralgias were more common in patients receiving romiplostim versus placebo.[43] Time to maximum response in healthy individuals is reported as 8 to 11 days for avatrombopag, 16 days for eltrombopag, and 12 to 14 days for romiplostim.[44-46]

Across trials of rituximab in adults, the weighted mean complete response rate (ie, platelet count >150 × 10^9/L) was 43.6% (95% CI, 29.5%-57.7%), and the weighted mean overall response rate (ie, platelet count ≥50 × 10^9/L) was 62.5% (95% CI, 52.6%-72.5%). Median time to response was 5.5 weeks. Toxicities of grade 3 or 4 severity occurred in 3.7% of patients; 2.9% died due to adverse events associated with rituximab.[47]

In a phase 3 study of fostamatinib, response (platelet count ≥50 × 10^9/L) within 12 weeks of initiating treatment occurred in 43% of patients and median time to response was 15 days. Diarrhea, hypertension, nausea, dizziness, and increased alanine aminotransferase were reported more frequently in patients receiving fostamatinib versus placebo.[48]

Other immune-modulating medications are also available to treat ITP; however, they have not been evaluated in randomized trials and evidence comes mainly from small, retrospective case series. In most reports, immune-modulating medications are added to corticosteroids with a goal of steroid reduction and cessation but with few data on subsequent time to corticosteroid withdrawl. These steroid-sparing medications include 6-mercaptopurine, azathioprine, cyclophosphamide, cyclosporine, danazol, dapsone, mycophenolate mofetil (MMF), and vinca alkaloids. Most of these medications have low response rates, ranging from 30% to 50%, with the exception of vinca alkaloids, which are reported to have a higher response rate of 70%, but with a short duration of response.[49] Response is observed within 1 week for vinca alkaloid treatment and within 1 to 2 weeks with cyclosporine; time to response is weeks to months for the other agents.[49] In some reports, treatment with these immune-modulating medications can induce long-term but unmaintained remissions; however, each has its own set of toxicities that can be quite severe. Recently, sirolimus has shown some promise for treatment of relapsed/refractory ITP, with a response rate of 85% in ITP patients after 3 months of treatment and 75.6% in patients with ITP or other autoimmune cytopenias after a median of 14 months' treatment and 18 months' follow-up; treatment was generally well tolerated.[50,51] The combination of danazol plus all-trans retinoic acid was recently evaluated in a phase 2 trial for second-line management of adults with primary ITP. After 52 weeks of follow-up, 38% of patients (20/45) achieved complete response versus 8% of patients (4/48) receiving danazol alone. Two grade 3 adverse events were observed in the trial.[52]

7 | STRATEGIES FOR LIMITING CORTICOSTEROID EXPOSURE

Given that corticosteroids are frequently used for an extended duration despite guideline recommendations, and that their use remains high in second- and third-line therapy,[38] it is crucial that strategies for limiting corticosteroid exposure be considered.

In first-line treatment, one strategy for limiting exposure is incorporation of TPO-RAs in combination with an initial course of corticosteroids. The combination of TPO-RA therapy plus corticosteroid therapy has the potential to decrease exposure to corticosteroids by 30% during the initial 4 weeks of treatment and is associated with a significantly lower likelihood (P = .003) of continued corticosteroid dependence for every 24 weeks of use in patients with ITP.[27] Another alternative to corticosteroid therapy is MMF. In a randomized trial of MMF for patients with ITP, the rate of treatment failure following randomization (ie, platelet count <30 × 10^9/L and need for second-line therapy) over a mean 18 months of follow-up was significantly lower with MMF versus corticosteroids (22% [n = 59] vs 44% [n = 61]; P = 0.006). Common adverse events in both the MMF and corticosteroid group included difficulty sleeping (35.6% vs 27.9%), mood changes (30.5% vs 34.4%), and weight gain (28.8% vs 34.4%).[53] Although pulsed dexamethasone therapy is intended to reduce exposure to long-term corticosteroid therapy, evidence is conflicting. One trial reported no reduction in overall corticosteroid exposure with pulsed dexamethasone versus prednisone,[21] while another trial reported a 40% reduction in overall exposure with pulsed dexamethasone.[24]

For patients who do not respond to first-line therapy or relapse after it is tapered, a second key strategy for limiting cumulative steroid exposure is to employ guideline-recommended second-line therapies such as TPO-RAs, rituximab, fostamatinib, other immune-modulating agents, or splenectomy rather than subjecting the patient to recurrent courses of corticosteroids.[2,3]

8 | CONCLUSIONS

Corticosteroids remain an important treatment option in adults with ITP therapy due to low cost, high initial response rates, and acceptable short-term tolerability. However, long-term or repeated use of corticosteroids is associated with substantial toxicity.[32,33] Guidelines recommend limiting the duration of corticosteroids to <6 weeks,[2,3] but real-world evidence suggests that cortciosteroids remain overused in the first line and beyond.[38-40] Strategies for curtailing overuse of corticosteroids include replacing corticosteroids with another agent or combining corticosteroids with a second agent in the first line as well as initiating treatments more suitable for long-term use in patients who require second-line therapy.[27,53]

Quality improvement efforts aimed at reducing corticosteroid overuse in adults with ITP should also be undertaken. Such efforts could include decision support at the point of care to remind providers about appropriate use of corticosteroids; order sets embedded in the electronic health record to provide guidance to clinicians on appropriate management; and quality metrics, potentially linked to reimbursement, that assess appropriateness of corticosteroid prescribing.

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AUTHOR CONTRIBUTIONS

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