High-dose dexamethasone compared with prednisone for previously untreated primary immune thrombocytopenia: a systematic review and meta-analysis

Siraj Mithoowani, Kathleen Gregory-Miller*, Jennifer Goy, Matthew C Miller, Grace Wang, Nastaran Noroozi, John G Kelton, Donald M Arnold*

Summary

Background Whether high-dose dexamethasone has long-term efficacy and safety in previously untreated patients with immune thrombocytopenia is unclear. We did a systematic review and a meta-analysis of randomised trials to establish the effect of high-dose dexamethasone compared with prednisone for long-term platelet count response.

Methods We searched MEDLINE, Embase, Cumulative Index of Nursing and Allied Health Literature, and the Cochrane Library Database for papers published from 1970 to July, 2016, and abstracts from American Society of Hematology annual meetings published from 2004 to 2015 for randomised trials comparing different corticosteroid regimens for patients with previously untreated immune thrombocytopenia who achieved a platelet count response. Trials that compared corticosteroids exclusively with other interventions were excluded. The primary endpoint was overall (platelets >30×10⁹/L) and complete (platelets >100×10⁹/L) platelet count response at 6 months with high-dose dexamethasone compared with standard-dose prednisone. Children and adults were analysed separately. Estimates of effect were pooled with a random-effects model.

Findings Nine randomised trials (n=1138) were included. Of those, five (n=533) compared one to three cycles of dexamethasone (40 mg per day for 4 days) with prednisone (1 mg per kg) for 14–28 days followed by dose tapering in adults. We found no difference in overall platelet count response at 6 months (pooled proportions 54% *vs* 43%, relative risk [RR] 1·16, 95% CI 0·79–1·71; p=0·44). At 14 days, overall platelet count response was higher with dexamethasone (79% *vs* 59%, RR 1·22, 95% CI 1·00–1·49; p=0·048). The dexamethasone group had fewer reported toxicities. Long-term response rates were similar when the data were analysed by cumulative corticosteroid dose over the course of treatment. No difference in initial platelet count response was observed with different high-dose corticosteroid regimens in children.

Interpretation In adults with previously untreated immune thrombocytopenia, high-dose dexamethasone did not improve durable platelet count responses compared with standard-dose prednisone. High-dose dexamethasone might be preferred over prednisone for patients with severe immune thrombocytopenia who require a rapid rise in platelet count.

Funding Canadian Institutes of Health Research, and Canadian Blood Services, and Health Canada.

Lancet Haematol 2016

Published Online
September 15, 2016
http://dx.doi.org/10.1016/S2352-3026(16)30109-0

See Online/Comment
http://dx.doi.org/10.1016/S2352-3026(16)30124-7

*Authors contributed equally

McMaster Centre for Transfusion Research (Prof J G Kelton MD, D M Arnold MD) **and Department of Medicine, Michael G DeGroote School of Medicine, McMaster University, Hamilton, ON, Canada** (S Mithoowani MD, K Gregory-Miller MD, J Goy MD, M C Miller MD, G Wang MMath, N Noroozi MD, Prof J G Kelton, D M Arnold)**; and Canadian Blood Services, Hamilton, ON, Canada** (D M Arnold)

Correspondence to:
Dr Donald M Arnold, HSC 3V-50, 1280 Main Street West, Hamilton, ON, Canada
arnold@mcmaster.ca

Introduction

Immune thrombocytopenia is a common autoimmune disease characterised by low platelet counts (<100 cells×10⁹/L) and an increased risk of bleeding. Guidelines[1] and consensus reports[2] recommend either high-dose dexamethasone or standard-dose prednisone as first-line therapy; however, there is debate about which dose of corticosteroid to use.[3] High-dose dexamethasone is administered as a short pulse, typically 40 mg per day consecutively for 4 days and repeated for one or two additional monthly cycles depending on the response noted by platelet count. This regimen has been reported to produce high, durable platelet count responses in observational studies;[4–6] however, one randomised trial has reported no difference in platelet count response at 6 months compared with prednisone.[7] Severe toxic effects were frequently reported with high-dose dexamethasone in some studies[8] but not in others.[7]

Dexamethasone is a corticosteroid that has an anti-inflammatory effect that is more than six times more potent than prednisone (40 mg of dexamethasone is equivalent to 250 mg of prednisone) with a longer biological half-life (36–72 h compared with 12–36 h).[9] Hence, any difference in efficacy or toxicity between the two approaches probably reflects differences in dosage rather than intrinsic properties of the drugs. Several studies, including one randomised trial in adults,[7] have shown that higher doses of corticosteroids can increase the platelet count more quickly; however, when faced with a new diagnosis of immune thrombocytopenia, clinicians and patients are most interested in treatments that can improve sustained remission.

We aimed to evaluate the long-term efficacy and safety of high-dose corticosteroids as an initial treatment for adults or children with previously untreated immune thrombocytopenia.

Research in context

Evidence before this study

Guidelines recommend either high-dose corticosteroids (eg, dexamethasone 40 mg orally per day for 4 days consecutively in one or more cycles) or standard-dose prednisone (1 mg/kg per day followed by a dose taper) as first-line treatment for adults with primary immune thrombocytopenia. Both regimens were considered equivalent. Observational studies have suggested that high-dose dexamethasone was effective at producing sustained platelet count responses in some patients with immune thrombocytopenia. Small comparative trials have evaluated the efficacy and safety of high-dose dexamethasone compared with prednisone.

Added value of this study

To our knowledge, our study represents the first meta-analysis of randomised trials comparing high-dose dexamethasone versus standard-dose prednisone for patients with newly diagnosed primary immune thrombocytopenia. Our pooled analysis showed no difference in durable platelet count responses in adults, but a higher rate of initial platelet count response without additional toxicity.

Implications of all the available evidence

High-dose dexamethasone might be preferred over prednisone for adults with severe immune thrombocytopenia who require a rapid rise in platelet count.

Methods

Search strategy and selection criteria

For this systematic review and a meta-analysis, we searched the electronic databases of MEDLINE, Embase, Cumulative Index of Nursing and Allied Health Literature, and the Cochrane Library Database for papers published in English from 1970 to July, 2016, with the following search terms: "idiopathic thrombocytopenic purpura", "immune thrombocytopenic purpura", "ITP", or "immune thrombocytopenia"; "randomized controlled trial", "controlled trial", "random allocation", "prospective study", and "clinical trial"; and "corticosteroids", "prednisone", "dexamethasone", and "steroids". We searched abstracts from the American Society of Hematology published from 2004 to 2015 with the online search engine and the terms "ITP" and "corticosteroids", "steroids", "prednisone", or "dexamethasone". Additional studies were identified by manually searching reference lists of primary studies and review articles. Study authors of full papers were contacted for additional information where required.

Randomised trials published in English that compared different corticosteroid dose regimens for the treatment of patients with previously untreated primary immune thrombocytopenia were included. Eligible studies reported the proportion of patients who achieved a platelet count response in each treatment group. Trials that compared corticosteroids with other interventions were excluded. KG-M and JG independently assessed study eligibility by screening titles, and reviewing abstracts and full text manuscripts in detail. Agreement between reviewers on initial study selection was measured with the κ statistic. Disagreements were resolved by consensus.

Data analysis

Data abstraction was done in duplicate by SM and KG-M. We collected corticosteroid type and dosing regimens, proportions of patients who had an overall or complete platelet count response, associated definitions of overall and complete response, number of bleeding events during follow-up, baseline demographic data, and toxic effects attributable to corticosteroids. We assessed the methodological quality of randomised trials with a validated tool[10] and assessed the risk of bias with the Cochrane Collaboration tool,[11] which is based on six criteria: sequence generation, allocation concealment, blinding of participants, blinding of outcomes, completeness of the data, and selective outcome reporting.

Long-term response was defined as the achievement of a platelet count of more than 30 cells×10^9/L (overall response) or more than 100 cells×10^9/L (complete response) at 6 months or longer without concomitant treatment. Initial response was based on the earliest platelet count measurement. The primary objective was to compare long-term platelet count responses (ie, overall and complete response) with high-dose dexamethasone (40 mg per day consecutively for 4 days) or standard-dose prednisone (1 mg/kg per day with a taper, typically over 4–6 weeks). Secondary objectives were to compare initial responses (within 14 days), toxicities of high-dose dexamethasone and standard-dose prednisone, and other corticosteroid regimens, which we designated as low, standard, or high dose on the basis of the initial corticosteroid dose converted to prednisone equivalent units per kg[9] (low dose ≤0·5 prednisone equivalent units per kg per day; standard dose >0·5 to <2·0 prednisone equivalent units per kg per day; and high dose ≥2 prednisone equivalent units per kg per day). Additionally, to establish platelet count response, we designated treatment groups as high or low dose on the basis of total corticosteroid exposure over the duration of the trial where possible.

We did a meta-analysis with random effects[12] to calculate pooled relative risks and pooled proportions on the basis of assumption that the true effect size of high-dose dexamethasone would vary between studies.[13,14] Heterogeneity was assessed with the I^2 statistic. Funnel plots and public trial registration were examined for publication bias.[15] Adults and children were analysed separately. Review Manager (version 5.3) was used for the analyses.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 2582 citations in our initial literature search. After excluding 1219 non-relevant titles, we reviewed 1363 abstracts and 306 full text articles in duplicate and independently (figure 1). We identified 12 randomised trials that compared different corticosteroid regimens. Of those, one study was excluded because it compared equivalent corticosteroid doses (prednisone 1 mg per kg per day *vs* deflazacort 1·4 mg per kg per day)[16] and two studies were excluded because they did not report platelet count response rates.[17,18] Thus, nine randomised trials in adults (n=809) and children (n=329) were included in this analysis. One trial was published in abstract form only.[19] Data from that study were provided directly from the study authors. Agreement between reviewers on articles selection was good (κ=0·72). Only the dexamethasone versus prednisone trials were amenable to meta-analysis because of their similar patient populations and study designs.

Five trials compared high-dose dexamethasone with prednisone in adults (n=533)[7,19–22] and of those, four trials[7,19–21] reported long-term outcomes (n=497; table 1). In total, 459 patients were assessable for long-term responses (38 patients were lost to follow-up)[19,20] and 484 patients were assessable for short-term responses (49 patients had incomplete short-term response data in one trial).[19] All studies used the same dose of dexamethasone (40 mg per day for 4 days) but the number of cycles ranged from one to three. In one trial, patients in the dexamethasone group were randomly assigned further to receive or not to receive maintenance dexamethasone (0·035 mg/per day) between cycles and for 3 months after the last cycle.[20] In another trial, one cycle of dexamethasone was administered followed by prednisolone 30 mg per day for 10 days.[22] For all trials, the dose of prednisone was 1 mg per kilogram body weight for 28 days except one trial in which the course of prednisone was 14 days.[22] Whether and how prednisone was tapered was not fully reported. Long-term responses were assessed at 6 months; initial responses were reviewed within 14 days in all trials except one which assessed responses at 28 days in the prednisone group only.[7] Two trials reported bleeding events as an outcome.[7,22]

Two trials compared standard-dose prednisone and low dose prednisone in a combined population of adults and children (n=480)[23,24] and two trials compared two different high-dose corticosteroid regimens and intravenous immunoglobulin in children only (n=125; table 2).[25,26] In the latter two trials, data were extracted only from the groups who received corticosteroids.

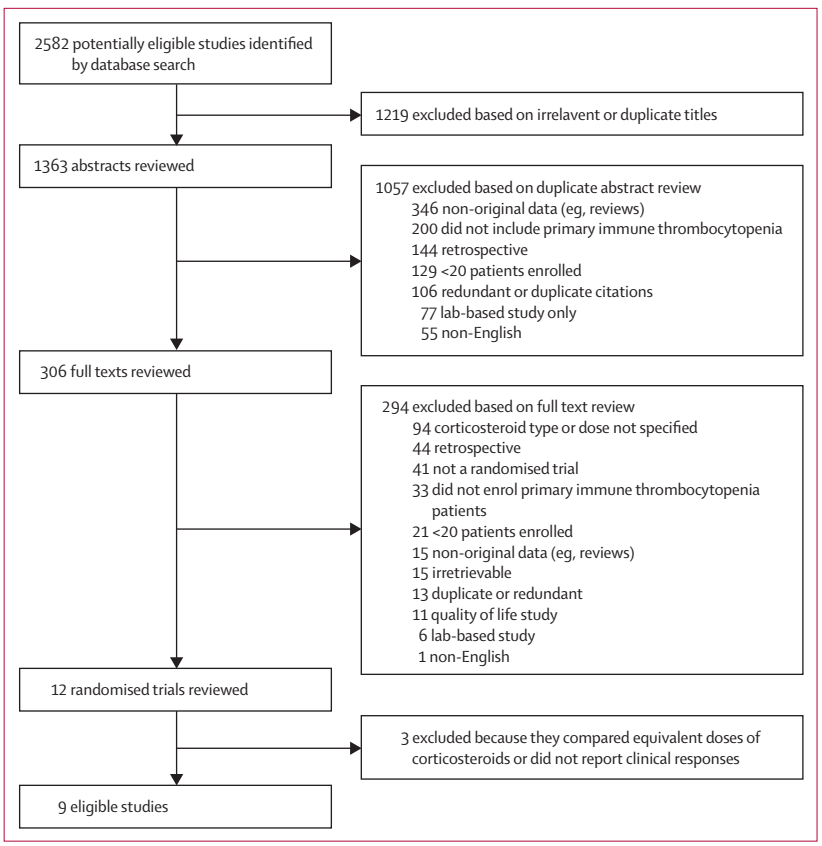

Figure 1: **Article search and selection**

Avoidance of rescue treatment was explicitly included in the definition of response in three trials and implicit in six trials. All patients were enrolled at initial presentation of immune thrombocytopenia, except for one study that included five patients with relapsed immune thrombocytopenia.[22] Mean or median platelet count at baseline in the primary trials ranged from 5–18×10⁹ platelets per L for children and 7–25×10⁹ platelets per L for adults.

The pooled proportion of overall platelet count response at 6 months was not different with 1–3 cycles of high-dose dexamethasone or standard-dose prednisone in adults previously untreated immune thrombocytopenia (pooled proportions 54% *vs* 43%; relative risk [RR] 1·16 [95% CI 0·79–1·71]; p=0·44; figure 2A, table 3). Similarly, there was no difference between groups in complete platelet count response at 6 months (37% *vs* 21%, RR 1·49 [95% CI 0·50–4·48]; p=0·48). The proportion of patients achieving an initial overall platelet count response (79% *vs* 59%, RR 1·22 [95% CI 1·00–1·49], p=0·048) or complete response (64% *vs* 36%, RR 1·67 [95% CI 1·02–2·72], p=0·040) by 14 days was higher in the dexamethasone group (figures 2B, 2C). In a sensitivity analysis excluding the abstract-only publication, the long-term treatment effect was unchanged, and initial response rates were more strongly in favour of

	n	Mean age (years)	Female sex (%)	Disease stage	Median duration of follow-up	Dexamethasone (40 mg/day for 4 days)	Prednisone (1 mg/kg per day)	Long-term response	Initial response
Wei (2015)[7]	192	44 (18–75)	136/192 (71%)	Newly-diagnosed	5 months	1 or 2 cycles*	28 days	6 months	10 days or 28 days†
Bae (2010)[19]	151	44 (··)	105/151 (70%)	Newly-diagnosed	··	1 or 2 cycles‡	28 days	6 months	7 days
Din (2014)[20]	94	30 (16–64)	50/90 (56%)	Newly-diagnosed	16 months	3 cycles§	28 days	6 months	14 days
Mashhadi (2012)[21]	60	26 (18–48)	47/60 (78%)	Newly-diagnosed	·· (range 12–48 months)	1 cycle	28 days	6 months	7 days
Praituan (2009)[22]	36	42 (··)	28/36 (78%)	Newly-diagnosed‖	6 months	1 cycle, followed by prednisolone 30 mg per day for 10 days	14 days¶	··	5 days

Data are mean (range) or n/N (%). Prednisone dosing does not include dose tapering. *Second cycle of dexamethasone was given if there was no response by day 10. †Initial response was assessed within 10 days in the dexamethasone group and within 28 days in the prednisone group. ‡Second cycle of dexamethasone was given if there was no response by 6 months. §With or without maintenance dexamethasone 0·035 mg/kg per day between 14 day cycles and for 3 months after the last cycle. ‖Five of 36 patients had relapsed.

Table 1: **Randomised trials of high-dose dexamethasone versus prednisone in adults**

	n	Control group	Experimental group
Bellucci (1988)[23]	207 adults; 143 children	Standard-dose prednisone 1·0 mg/kg per day for 3 weeks	Low-dose prednisone 0·25 mg/kg per day for 3 weeks
Mazzucconi (1985)[24]	69 adults; 61 children	Standard-dose prednisone 1·5 mg/kg per day until positive response	Low-dose prednisone 0·5 mg/kg per day until positive response
Fujisawa (2000)[26]	0 adults, 87 children	High-dose prednisone 2·0 mg/kg per day for 14 days	High-dose intravenous methylprednisolone 5·0 mg/kg per day for 5 days or 30·0 mg/kg per day for 3 days
Albayrak (1994)[25]	0 adults, 38 children	High-dose oral methylprednisolone 30·0 mg/kg per day for 7 days	High-dose oral methylprednisolone 50·0 mg/kg per day for 7 days

High dose was classified as greater than or equal to 2·0 prednisone equivalent units per day (ie, ≥2 mg/kg of prednisone per day). Standard dose was classified as >0·5 to <2·0 prednisone-equivalent units (eg, 1 mg/kg of prednisone per day); low dose was classified as less than or equal to 0·5 prednisone-equivalent units per day.

Table 2: **Randomised trials of different corticosteroid regimens in adults and children**

See Online for appendix

dexamethasone for overall responses (RR 1·32 [95% CI 1·04–1·69], p=0·010) and complete responses (RR 2·09 [95% CI 1·54–2·82], p<0·0001; appendix p 9).

We analysed the effect of cumulative corticosteroid dose in adults from three trials that reported total corticosteroid exposure in sufficient detail during 6 months of observation (n=238).[19–21] Mean cumulative doses in the high-dose group were 40 prednisone-equivalent units per kg of bodyweight and in the low-dose groups were 25 prednisone-equivalent units per kg of bodyweight (assuming an average adult weight of 70 kg). High cumulative doses were not associated with improved overall long-term platelet count response (RR 1·18 [95% CI 0·53–2·62], p=0·68).

No difference in long-term or initial responses was observed with low-dose or standard-dose prednisone in adults or children in either of the two trials that compared these groups (appendix pp 3,4).[23,24] No difference in initial responses was observed with different high-dose corticosteroid regimens in children in both trials that compared these groups (long term responses were not reported; appendix p 5).[25,26]

In the two trials reporting bleeding events,[7,22] high-dose dexamethasone was associated with less bleeding in the first 10 days of follow-up (13 events in 113 patients who received high-dose dexamethasone compared with 28 events in 115 patients who received standard-dose prednisone).

Two trials were preregistered in a clinical trials database.[7,19] Funnel plots did not suggest that small, positive trials were over-represented (appendix p 6, 7). The risk of bias was low in two trials that had concealed randomisation and minimal losses to follow up (appendix p 1).[7,22] For the other trials, risk of bias was judged to be unclear (n=4) or high (n=3). A sensitivity analysis was done excluding the three trials with high risk of bias and the findings were unchanged (appendix p 8).

Adverse events attributable to corticosteroids were reported in five trials that compared high-dose dexamethasone and standard-dose prednisone in adults (n=529 patients).[7,19–22] The most common adverse events were weight gain and cushingoid features, gastrointestinal symptoms, hyperglycaemia, and insomnia (table 4); weight gain and cushingoid features were less common with high-dose dexamethasone. Overall, there were 67 adverse events reported in 280 patients who received high-dose dexamethasone, compared with 115 adverse events in 249 patients who received standard-dose prednisone (some patients had more than one adverse event). This translated to 24 adverse events per 100 patients in the dexamethasone group and 46 adverse events per 100 patients in the prednisone group. One out of every five adverse events in the prednisone group was weight gain. There were four infections documented in the prednisone group and none in the dexamethasone group (two trials

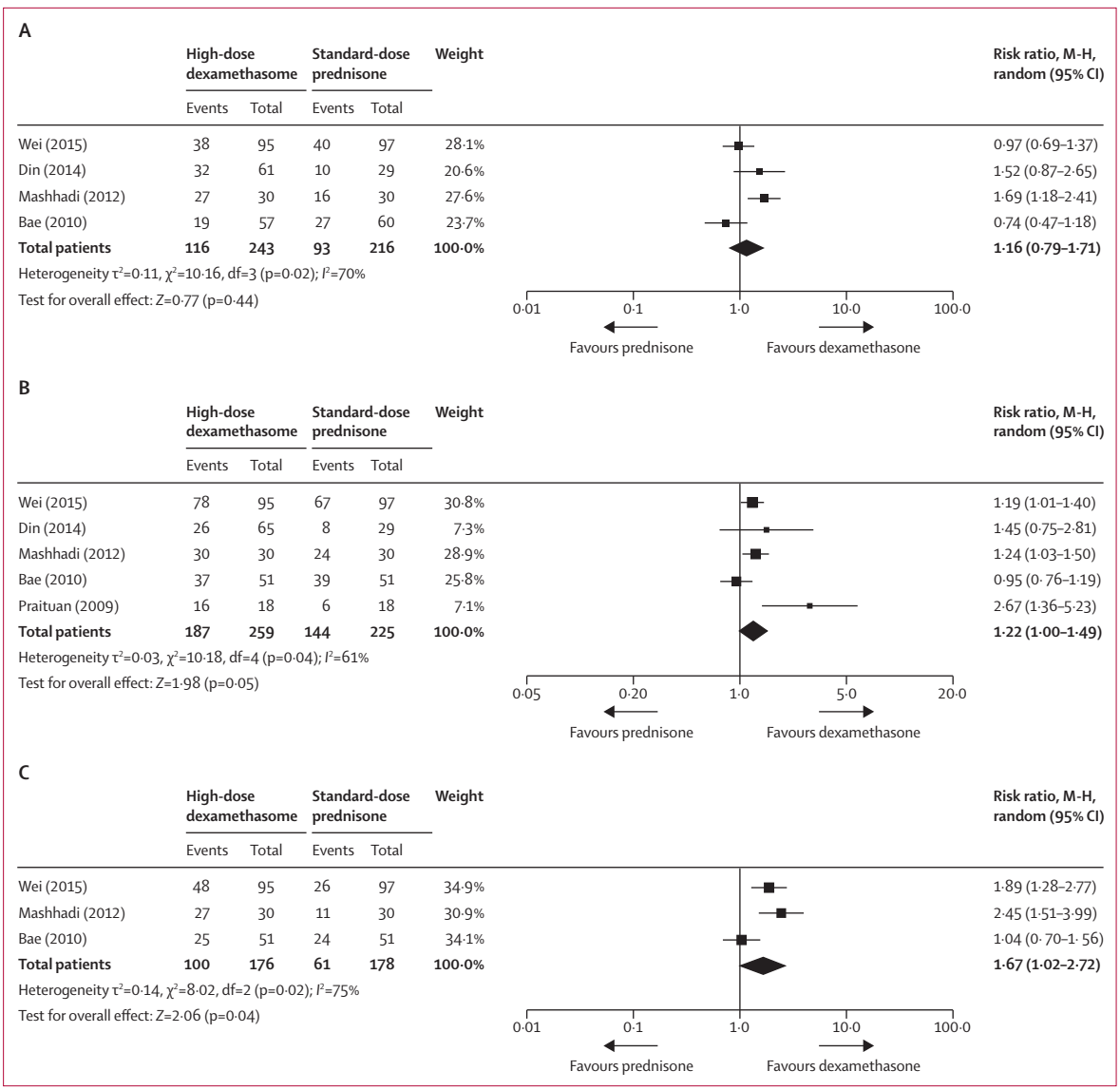

Figure 2: **Platelet count responses in adults after treatment with high-dose dexamethasone versus standard-dose prednisone**
(A) Overall response at 6 months or longer after treatment. (B) Overall response within 14 days of treatment. One trial assessed initial response at 10 days in the dexamethasone group and at 28 days in the prednisone group.[7] (C) Complete response within 14 days of treatment. One trial assessed initial response at 10 days in the dexamethasone group and at 28 days in the prednisone group.[7] M-H=Mantel-Haenszel.

reported this outcome).[7,19] Nine patients discontinued treatment due to toxic effects: four patients who receiving dexamethasone and five patients who received prednisone. Reasons for discontinuation of treatment were pneumonia, hyperglycaemia, myalgia, vomiting, and hypertension.[7,19,20] All four patients who discontinued treatment early in the dexamethasone group did so after completing one course of treatment. The amount of prednisone received by the five patients who stopped treatment was not reported.[20]

Adverse events were frequent in the two trials that compared different regimens of very-high-dose corticosteroids with intravenous immunoglobulin in children (appendix p 2).[25,26] In one trial that compared oral methylprednisolone 30 mg/kg per day for 7 days versus 50 mg/kg per day for 7 days, all patients in the corticosteroid groups had increased appetite and cushingoid appearance.[25]

Discussion

Pooling data from randomised trials, we found no difference in platelet count response at 6 months in adults treated with high-dose dexamethasone or standard-dose prednisone; however, responses occurred more rapidly with high-dose dexamethasone without additional toxicities. In children, initial platelet count response rates were similar with various high-dose corticosteroid regimens.

	n	Mean age (years)	Long-term response (6 months; %)		Initial response (5–14 days; %)	
			Dexamethasone	Prednisone	Dexamethasone	Prednisone
Wei (2015)[7]	192	44 (18–75)	38/95 (40%)	40/97 (41%)	78/95 (82%)	67/97 (69%)*
Bae (2010)[19]	151	44 (··)	19/57 (33%)	27/60 (45%)	37/51 (73%)	39/51 (76%)
Din (2014)[20]	94	30 (16–64)	32/61 (52%)	10/29 (34%)	26/65 (40%)†	8/29 (28%)†
Mashhadi (2012)[21]	60	26 (18–48)	27/30 (90%)	16/30 (53%)	30/30 (100%)	24/30 (80%)
Praituan (2009)[22]	36	42 (··)	··	··	16/18 (89%)	6/18 (33%)

Data are mean (range) or events/patients (%). Dexamethasone dose was 40 mg per day for 4 consecutive days in one to three cycles. Prednisone dose was 1 mg/kg per day for 14 to 28 days. *Initial response was assessed at 28 days in the prednisone group. †Initial response was assessed later (14 days) than the other studies (median 7 days).

Table 3: **Overall platelet count responses in randomised trials of dexamethasone versus prednisone in adults**

	All patients (n=529)	High-dose dexamethasone (n=280)	Standard-dose prednisone (n=249)
Cushingoid appearance	13 (2%)	0	13 (5%)
Weight gain	28 (5%)	5 (2%)	23 (9%)
Oedema	4 (1%)	0	4 (2%)
Gastrointestinal toxicities (eg, peptic ulcer, nausea, or diarrhoea)	34 (6%)	14 (5%)	20 (8%)
Hyperglycaemia	30 (6%)	14 (5%)	16 (6%)
Insomnia or fatigue	18 (3%)	9 (3%)	9 (4%)
Hypertension	17 (3%)	6 (2%)	11 (4%)
Anxiety or mood disorders	13 (2%)	9 (3%)	4 (2%)
Dizziness	7 (1%)	2 (1%)	5 (2%)
Acne	6 (1%)	4 (1%)	2 (1%)
Infection	4 (1%)	0	4 (2%)
Myalgia and arthralgia	3 (1%)	0	3 (1%)
Palpitations	3 (1%)	2 (1%)	1 (<1%)
Fever	1 (<1%)	1 (<1%)	0
Elevated liver enzymes	1 (<1%)	1 (<1%)	0
Total adverse events*	182	67	115
Patients who discontinued treatment because of toxicities	9 (2%)	4 (1%)	5 (2%)

*Patients might have been counted more than once in the summary of total adverse events.

Table 4: **Adverse events reported in trials comparing high-dose dexamethasone and standard-dose prednisone in adults**

It is hypothesised that pulse high-dose corticosteroids might have a fundamentally different effect on the autoimmune response to platelets than prednisone administered over a more protracted course. Laboratory studies have shown that high-dose dexamethasone can ameliorate the immune defects in immune thrombocytopenia by regulating interleukin-22 production and correcting T-helper-1 cell and T-helper-22 cell polarisation,[27] improving interleukin-10 secretion by CD5 positive B cells,[28] inhibiting Fc-γreceptors on monocytes,[29] and correcting abnormal T-cell subsets.[30] Such in-vitro studies provided a biological rationale for clinical trials; however, as our analysis shows, durable clinical outcomes were similar with either regimen. Our results support findings of a previous study[31] showing that the choice of initial corticosteroid probably does not impact the natural history of immune thrombocytopenia in adults.

Several observational studies reported that high-dose dexamethasone was associated with a high rate of durable platelet count responses.[4–6] A study of 125 adults with previously untreated immune thrombocytopenia reported that a single course of high-dose oral dexamethasone resulted in 53 (42%) of 125 patients who achieved a sustained response at 6 months and 106 (85%) of 125 patients who achieved an initial response.[4] Two prospective pilot studies subsequently assessed repeated cycles of pulse dexamethasone in adults:[5] a single centre study (n=37) of six cycles of high-dose dexamethasone administered every 4 weeks showed a 90% relapse-free survival at 15 months and an 89% initial response rate (33 of 37 patients);[5] and a multicentre study (n=48 adults) of four cycles administered every 2 weeks reported that 32 (66%) of 48 patients achieved a sustained response (defined as a response lasting at least 2 months after treatment discontinuation) and that 41 (85%) of 48 patients achieved an initial response.[5] In our analyses, the pooled proportion for sustained response at 6 months was 54% after one to three cycles of high-dose dexamethasone, which lies between the response rates reported in observational studies that used one or multiple cycles noted previously.

As a secondary endpoint, we showed an improvement in initial platelet count responses with high-dose dexamethasone. Our results showed a 79% initial overall response rate with dexamethasone, which is similar to what has been observed in previous observational studies.[4,5] Compared with prednisone, the relative risk for rapid overall response was 1·22 with the lower bound of the confidence limit reaching 1·00. This effect became larger (RR 1·32, 95% CI 1·04–1·69) when we excluded the study that was presented in abstract form only.

We found that adverse events were reported less frequently with high-dose dexamethasone. A formal analysis of toxicities by cumulative dose was not possible; however, cumulative corticosteroid exposures were generally lower with dexamethasone than with prednisone. Treatment related toxicities might not have been fully reported in randomised trials because of highly selected patient populations, relatively short follow-up periods, and limited reporting of adverse events.[32] Moreover, short-lived side-effects associated with pulse corticosteroids (eg, insomnia or mood changes) might not be reported as reliably as long-term toxicities from prednisone such as weight gain. Prednisone tapering was incompletely reported and therefore toxicities in the prednisone group might be related to prolonged tapering schedules. It is possible that shorter courses of prednisone (ie, 14–21 days)[22,31]

with well-defined tapering regimens would be better tolerated. Of the seven trials that reported adverse events, only two reported infections and neither provided specific information on the causative organisms.[7,19]

A strength of our study was the inclusion of randomised trials only, which avoided biases inherent to observational studies. We reported outcomes for both adults and children and did separate analyses for both populations. We converted corticosteroid doses to prednisone equivalent units to allow for meaningful comparisons across different treatment regimens. A priori, we considered that differences in cumulative corticosteroid exposure might explain differences in long-term platelet count responses; however, this effect was not observed in our analysis. A limitation was that many trials did not report overall corticosteroid exposure during the course of treatment, including details of rescue treatments and prednisone tapering schedules.[7,23,24] Trials varied in their definitions of response, in terms of platelet count thresholds and of timings of evaluation especially for short-term responses, which were assessed within 5–14 days in most trials. Our study did not address the effect of a combination of corticosteroids with other treatments such as thrombopoietin receptor agonists[33] or rituximab;[34] a strategy which has previously been shown to be effective.[35,36]

In summary, we found that durable platelet count responses were not different with high-dose dexamethasone or standard-dose prednisone in adults with previously untreated immune thrombocytopenia. High-dose dexamethasone was associated with improved platelet count responses by 14 days in adults, fewer bleeding events, and less toxicity than prednisone over the course of treatment. Another advantage is that the regimen is short, lasting only 4 days, as opposed to prednisone, which is often continued as a protracted course of therapy resulting in high corticosteroid exposures. In randomised trials, dexamethasone was administered in one to three cycles over a 6 month period, which is a reasonable maximal dose. High-dose dexamethasone might be preferred over prednisone for patients with severe immune thrombocytopenia who require a rapid rise in platelet count (eg, for severe bleeding) in conjunction with other treatments that work even faster such as intravenous immunoglobulin.[37] Additional high-quality randomised trials are needed to establish the optimum corticosteroid dose regimen and to assess overall impact on quality of life.

Contributors

SM, KG-M, JG, MCM, NN, and DMA contributed to the original concept. SM, KG-M, JG, MCM, GW, and DMA contributed to data collection and analysis. The manuscript was drafted by SM, KG-M, and DMA, and all authors provided major intellectual contributions to the manuscript, reviewed and revised its content, and approved the final version.

Declaration of interests

We declare no competing interests.

Acknowledgments

Financial support was provided by the Canadian Institutes of Health Research and Canadian Blood Services (Grant #349981). DMA holds the JG Kelton Chair in Translational Research from McMaster University.

References

1 Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 2011; **117:** 4190–207.
2 Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010; **115:** 168–86.
3 Cuker A, Prak ETL, Cines DB. Can immune thrombocytopenia be cured with medical therapy? *Semin Thromb Hemost* 2015; **41:** 395–404.
4 Cheng Y, Wong RSM, Soo YOY, et al. Initial treatment of immune thrombocytopenic purpura with high-dose dexamethasone. *N Engl J Med* 2003; **349:** 831–36.
5 Mazzucconi MG, Fazi P, Bernasconi S, et al. Therapy with high-dose dexamethasone (HD-DXM) in previously untreated patients affected by idiopathic thrombocytopenic purpura: a GIMEMA experience. *Blood* 2007; **109:** 1401–07.
6 Andersen JC. Response of resistant idiopathic thrombocytopenic purpura to pulsed high-dose dexamethasone therapy. *N Engl J Med* 1994; **330:** 1560–64.
7 Wei Y, Ji XB, Wang YW, et al. High-dose dexamethasone vs prednisone for treatment of adult immune thrombocytopenia: a prospective multicenter randomized trial. *Blood* 2016; **127:** 296–302.
8 Warner M, Wasi P, Couban S, Hayward C, Warkentin T, Kelton JG. Failure of pulse high-dose dexamethasone in chronic idiopathic immune thrombocytopenia. *Am J Hematol* 1997; **54:** 267–70.
9 Brunton L, Lazo J, Parker K. Goodman & Gilman's the pharmacological basis of therapeutics, Eleventh Edition. New York: McGraw-Hill Education, 2005.
10 Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17:** 1–12.
11 Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343:** d5928.
12 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7:** 177–88.
13 Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010; **1:** 97–111.
14 Greenland S. Quantitative methods in the review of epidemiologic literature. *Epidemiol Rev* 1987; **9:** 1–30.
15 Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 2001; **54:** 1046–55.
16 Ferrari A, Pasqualetti D, Del Bianco P, Gandolfo GM, Chistolini A, Mazzucconi MG. Prednisone versus deflazacort in the treatment of autoimmune thrombocytopenic purpura: evaluation of clinical response and immunological modifications. *Haematologica* 1991; **76:** 342–45.
17 Khalifa AS, Tolba KA, el-Alfy MS, Gadallah M, Ibrahim FH. Idiopathic thrombocytopenic purpura in Egyptian children. *Acta Haematol* 1993; **90:** 125–29.
18 Matschke J, Müller-Beißenhirtz H, Vester I, et al. A randomized tial of daily prednisone versus pulsed dexamethasone in treatment naïve patients with idiopathicthrombocytopenic purpura. *Blood* 2013; **122:** 325.
19 Bae SH, Ryoo HM, Lee WS, et al. High dose dexamethasone vs. conventional dose prednisolone for adults with immune thrombocytopenia: a prospective multicenter phase III trial. *Blood* 2010; **116:** 3687.
20 Din B, Wang X, Shi Y, Li Y. Long-term effect of high-dose dexamethasone with or without low-dose dexamethasone maintenance in untreated immune thrombocytopenia. *Acta Haematol* 2015; **133:** 124–28.
21 Mashhadi MA, Kaykhaei MA, Sepehri Z, Miri-Moghaddam E. Single course of high dose dexamethasone is more effective than conventional prednisolone therapy in the treatment of primary newly diagnosed immune thrombocytopenia. *Daru* 2012; **20:** 7.

22 Praituan W, Rojnuckarin P. Faster platelet recovery by high-dose dexamethasone compared with standard-dose prednisolone in adult immune thrombocytopenia: a prospective randomized trial. *J Thromb Haemost* 2009; **7:** 1036–38.

23 Bellucci S, Charpak Y, Chastang C, Tobelem G. Low doses v conventional doses of corticoids in immune thrombocytopenic purpura (ITP): results of a randomized clinical trial in 160 children, 223 adults. *Blood* 1988; **71:** 1165–69.

24 Mazzucconi MG, Francesconi M, Fidani P, et al. Treatment of idiopathic thrombocytopenic purpura (ITP): results of a multicentric protocol. *Haematologica* 1985; **70:** 329–36.

25 Albayrak D, Işlek I, Kalaycí AG, Gürses N. Acute immune thrombocytopenic purpura: a comparative study of very high oral doses of methylprednisolone and intravenously administered immune globulin. *J Pediatr* 1994; **125:** 1004–07.

26 Fujisawa K, Iyori H, Ohkawa H, et al. A prospective, randomized trial of conventional, dose-accelerated corticosteroids and intravenous immunoglobulin in children with newly diagnosed idiopathic thrombocytopenic purpura. *Int J Hematol* 2000; **72:** 376–83.

27 Cao J, Chen C, Li L, et al. Effects of high-dose dexamethasone on regulating interleukin-22 production and correcting Th1 and Th22 polarization in immune thrombocytopenia. *J Clin Immunol* 2012; **32:** 523–29.

28 Hua F, Ji L, Zhan Y, et al. Pulsed high-dose dexamethasone improves interleukin 10 secretion by CD5+ B cells in patients with primary immune thrombocytopenia. *J Clin Immunol* 2012; **32:** 1233–42.

29 Liu X-g, Ma S-h, Sun J-z, et al. High-dose dexamethasone shifts the balance of stimulatory and inhibitory Fcgamma receptors on monocytes in patients with primary immune thrombocytopenia. *Blood* 2011; **117:** 2061–69.

30 Li J, Wang Z, Hu S, Zhao X, Cao L. Correction of abnormal T cell subsets by high-dose dexamethasone in patients with chronic idiopathic thrombocytopenic purpura. *Immunol Lett* 2013; **154:** 42–48.

31 Godeau B, Chevret S, Varet B, et al. Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial. *Lancet* 2002; **359:** 23–29.

32 Cook D, Lauzier F, Rocha MG, Sayles MJ, Finfer S. Serious adverse events in academic critical care research. *CMAJ* 2008; **178:** 1181–84.

33 Gómez-Almaguer D, Herrera-Rojas MA, Jaime-Pérez JC, et al. Eltrombopag and high-dose dexamethasone as frontline treatment of newly diagnosed immune thrombocytopenia in adults. *Blood* 2014; **123:** 3906–08.

34 Chugh S, Darvish-Kazem S, Lim W, et al. Rituximab plus standard of care for treatment of primary immune thrombocytopenia: a systematic review and meta-analysis. *Lancet Haematol* 2015; **2:** e75–81.

35 Zaja F, Baccarani M, Mazza P, et al. Dexamethasone plus rituximab yields higher sustained response rates than dexamethasone monotherapy in adults with primary immune thrombocytopenia. *Blood* 2010; **115:** 2755–62.

36 Gudbrandsdottir S, Birgens HS, Frederiksen H, et al. Rituximab and dexamethasone vs dexamethasone monotherapy in newly diagnosed patients with primary immune thrombocytopenia. *Blood* 2013; **121:** 1976–81.

37 Arnold DM. Bleeding complications in immune thrombocytopenia. *Hematology Am Soc Hematol Educ Program* 2015; **2015:** 237–42.