European Journal of Internal Medicine 37 (2017) e23–e25

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Letter to the Editor

Response of first line treatment with corticosteroids in a population-based cohort of adults with primary immune thrombocytopenia

Keywords:
Epidemiology
Corticosteroids
ITP
Population-based
Treatment response

Despite therapeutic achievements like rituximab and thrombopoeitin receptor agonists, corticosteroids remain the mainstay of first line treatment for immune thrombocytopenia (ITP) [1,2]. However, only few randomized trials have been performed on steroids [3–7] and data on sustainability of response are conflicting. Pulsed high dose (HD) dexamethasone has been suggested to have higher response rates than standard treatment with prednisone but response is temporary [7]. Results on corticosteroid response among unselected adults are lacking. In this study we focus on response rates of prednisolone from an unselected population-based cohort of adult ITP patients.

The population-based cohort included all newly diagnosed adult primary ITP patients in a Danish county of Funen, with platelets below 100×10^9/l, and has been described in detail previously [8]. In brief, primary ITP patients were 15 years or older, residents in Funen, and diagnosed at any Danish hospital or out-patient clinic 1973–95. Patients were identified through their diagnosis codes in the Funen Patient Administrative System and Danish National Patient Registry [9] and the primary ITP diagnosis was subsequently verified by review of medical records. Patients were treated and followed without any pre-specified protocol according to the discretion of the physician. Extracted data included age, sex, platelet count and bleedings at diagnosis, response to treatment during the first six weeks, medical treatments, splenectomy, and platelet count and ITP treatment at last follow-up. Bleedings were categorized as present or absent from medical records; Cutaneous bleeding included petechiae or ecchymosis, and mucosal bleedings included epistaxis, vaginal bleeding, haematuria or rectal bleeding.

Since bleeding symptoms were registered only at diagnosis recent response criteria were not applied [10]. A complete response was therefore defined as platelets increasing to at least 100×10^9/l, and a partial response as an increase by ≥50% to 50–99 $\times 10^9$/l, or ≥100% to 20–49 $\times 10^9$/l. Platelet responses were assessed as the highest value during the first six weeks. Platelet count and ITP medication was also recorded as last follow-up, but response criteria was not applied at this time point since it was variable.

Patients were categorized into groups based on ITP treatment the first two weeks. Prednisolone monotherapy was categorized as such and prednisolone combined with other immunosuppressants was categorized as combination primary therapy. The initial therapeutic groups were after the first two weeks assigned subgroups based on the subsequent therapeutic strategies including secondary medical therapy (azathioprine, cyclophosphamide, vincristine, danazole, IvIG, cyclosporine) and splenectomy. Patients who remained without treatment were categorized as *No therapy*.

The ITP patients comprise 139 females (63%) and 82 males (37%) with a median age of 56.4 years, and a median platelet count of 12×10^9/l (IQR: 4–33). They presented with mucosal and skin bleedings (n = 91, 41%), skin bleeding only (n = 84, 38%), or no bleeding symptoms (n = 46, 21%). Prednisolone monotherapy during the first two weeks of treatment were given to 153 (69%), 14 (6%) received combination treatment, and 54 (24%) remained without treatment. More patients with combination treatment had mucosal bleeding symptoms and platelet counts were lower (Table 1). During the first six weeks patients received a mean of 1900 mg and 3130 mg prednisolone in the monotherapy and combination primary therapy groups, respectively (Table 1).

After the first two weeks 82 of 153 patients (54%) remained on prednisolone monotherapy treatment, 12 (8%) received second line medical regimens, 46 (30%) were splenectomized without new medical treatment, and 13 (8%) were treated with second line medical regimens and subsequently splenectomized (Table 1). Patients who remained on prednisolone monotherapy had comparable platelet counts and bleeding symptoms at diagnosis compared to patients who were later administered a second line medical or surgical treatment (Table 1).

During the first six weeks of treatment most patients achieved a platelet count response and only 15 (9.8%) patients with prednisolone monotherapy remained without response (Table 2). At last follow-up, 168 patients had discontinued medical treatment. Among the 82 patients who were treated with prednisolone monotherapy 46 (56%) remained with platelet counts ≥100×10^9/l without further treatment (Table 2). This corresponded to 28% of all treated patients, and 21% of the whole cohort. Almost all patients assigned second line medical treatment continued on immunosuppressive treatment if they were not later splenectomized (Table 2).

In our study including a large group of unselected adult ITP patients 70–80% of the patients treated with prednisolone monotherapy achieved an initial platelet count above 100×10^9/l that persisted after the discontinuation of steroid among 20–30%, in line with other results [4;5;7]. However within the subgroup of patients who were selected for monotherapy prednisolone treatment long term response rates was up to 50%. Response rates in previous trials with a comparator have shown no improved long-term response rates of short courses of HD corticosteroids compared to longer courses which may also have severe side effects [4;7]. During the first six weeks our patients who remained on prednisolone received an equivalent of the steroid dose in two pulsed series of dexamethasone 40 mg/day for four days using a potency factor of seven.

Despite the unselected nature our data have limitations. The data were retrospectively collected and therefore response assessment could not be done at a fixed last follow-up time point. This may have

http://dx.doi.org/10.1016/j.ejim.2016.09.001
0953-6205/© 2016 European Federation of Internal Medicine. Published by Elsevier B.V. All rights reserved.

Table 1
Characteristics of 221 adult primary ITP patients according to groups of therapeutic strategies during the first two weeks after diagnosis (primary treatment) and during the course of follow-up. Numbers are means ± standard deviation if not otherwise specified.

	Therapeutic groups — primary treatment		
	Prednisolone monotherapy n = 153	Combination primary therapy,* n = 14	No therapy, n = 54
Age at diagnosis	53.1 ± 19.5	57.1 ± 25.5	54.8 ± 19.5
Females — n (%)	102 (66.7)	5 (35.7)	32 (59.3)
Bleeding symptoms at diagnosis — n (%)	135 (88.2)	11 (78.6)	29 (53.7)
No bleeding	18 (11.8)	3 (21.4)	25 (46.3)
Skin bleeding only	62 (40.5)	1 (7.2)	21 (38.9)
Mucosal bleeding	73 (47.7)	10 (71.4)	8 (14.8)
Platelet count at diagnosis × 10^9/l	15.5 ± 18.4	11.1 ± 15.5	44.1 ± 27.4
Cumulated prednisolone (mg) first six weeks	1900 ± 1000	3130 ± 1131	–

	Therapeutic groups during course of follow-up						
	Prednisolone monotherapy, n = 82	Prednisolone and secondary medical§ therapy, n = 12	Prednisolone and splenectomy, n = 46	Prednisolone, secondary medical therapy§, and splenectomy, n = 13	Combination primary treatment* ± secondary § medical therapy (n = 8)†	Combination primary treatment* ± secondary§ medical therapy, and splenectomy (n = 6)‡	No therapy, n = 54
Age at diagnosis	56.6 ± 22.5	75.9 ± 11.0	38.0 ± 16.7	63.6 ± 19.1	66.9 ± 20.9	44.1 ± 27.0	54.8 ± 19.5
Females — n (%)	56 (68.3)	7 (58.3)	30 (65.2)	9 (69.2)	3 (37.5)	2 (33.3)	32 (59.3)
Bleeding symptoms at diagnosis — n (%)	70 (85.4)	11 (91.7)	43 (93.5)	11 (84.6)	6 (75.0)	5 (83.3)	29 (53.7)
No bleeding	12 (14.6)	1 (8.3)	3 (6.5)	2 (15.4)	2 (25.0)	1 (16.7)	25 (46.3)
Skin bleeding only	28 (34.2)	6 (50.0)	23 (50.0)	5 (38.4)	0 (0.0)	1 (16.7)	21 (38.9)
Mucosal bleeding	42 (51.2)	5 (41.7)	20 (43.5)	6 (46.2)	6 (75.0)	4 (66.6)	8 (14.8)
Platelet count at diagnosis × 10^9/l	17.3 ± 22.0	13.9 ± 13.8	12.4 ± 11.0	16.3 ± 18.9	15.5 ± 19.1	5.2 ± 6.1	44.1 ± 27.4
Cumulated prednisolone (mg) first six weeks	1702 ± 943	2447 ± 1500	1917 ± 873	2570 ± 918	3493 ± 1246	2707 ± 902	–

* Additional immunosuppressive therapy combined with corticosteroids such as IvIG or vincristine.
§ Secondary medical therapy includes any new non-surgical therapy introduced after first two weeks including azathioprine, cyclophosphamide, vincristine, danazole, IvIG, cyclosporine.
† 3 patients received only combination primary treatment, 5 were treated with secondary medical regimens also.
‡ 3 patients received combination primary treatment followed by splenectomy, 3 were treated also with secondary medical regimens before splenectomy.

introduced a bias since patients with short follow-up have a lower chance of being in remission. Since we focus on the prednisolone only treated patients we believe that this is not a major limitation although it may have made the estimate of patient in remission at last follow-up conservative. Also there was no systematic registration of corticosteroid toxicity despite the considerable accumulated dose of prednisolone. We conclude that longer course prednisolone monotherapy remains a valid first line adult ITP treatment. However, our study also

Table 2
Platelet count responses during first six weeks and at last follow-up among 221 adult primary ITP patients. Responses are stratified according to groups of therapeutic strategies during the first two weeks after diagnosis and during the course of follow-up. The numbers are counts and percentages within the platelet count response category (rows).

	Platelet (Pl) count (× 10^9/l) during first 6 weeks			
	Pl increases to ≥100	Pl increases to 50–99 by at least 50% or to 20 by at least 100%	No platelet count increase	Missing/not assessed
Therapy — first two weeks				
Prednisolone monotherapy	110 (71.9)	22 (14.4)	15 (9.8)	6 (3.9)
Combination primary therapy	7 (50.0)	4 (28.6)	3(21.4)	0 (0.0)
No therapy	15 (27.8)	1 (1.9)	0 (0.0)	38 (70.4)
Therapeutic course during follow-up				
Prednisolone monotherapy	65 (79.3)	8 (9.8)	7 (8.5)	2 (2.4)
Prednisolone and secondary medical therapy	7 (58.3)	3 (25.0)	1 (8.3)	1 (8.3)
Prednisolone and splenectomy	33 (71.7)	6 (13.0)	4 (8.7)	3 (6.5)
Prednisolone, secondary medical therapy, and splenectomy	5 (38.5)	5 (38.5)	3 (23.1)	0 (0.0)
Combination primary therapy	4 (50.0)	2 (25.0)	2 (25.0)	0 (0.0)
Combination primary therapy and splenectomy	3 (50.0)	2 (33.3)	1 (16.7)	0 (0.0)
No therapy	15 (27.8)	1 (1.9)	0 (0.0)	38 (70.4)
All	132 (59.7)	27 (12.2)	18 (8.1)	44 (19.9)

	Platelet (Pl) count (× 10^9/l) and treatment at last follow-up						
	Pl ≥ 100	Pl ≥ 100 with ongoing therapy	Pl 20–99	Pl 20–99 with ongoing therapy	Pl < 20	Pl < 20 with ongoing therapy	
Therapeutic course during follow-up							
Prednisolone monotherapy	46 (56.1)	12 (14.6)	13 (11.0)	8 (9.8)	2 (2.4)	3 (3.7)	0 (0.0)
Prednisolone and secondary medical therapy	0 (0.0)	8 (66.7)	1 (8.3)	3 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prednisolone and splenectomy	34 (73.9)	7 (15.2)	2 (4.4)	3 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)
Prednisolone, secondary medical therapy, and splenectomy	8 (61.5)	2 (15.2)	2 (15.2)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)
Combination primary therapy only	1 (12.5)	3 (37.5)	1 (12.5)	2 (25.0)	0 (0.0)	1 (12.5)	0 (0.0)
Combination primary therapy and splenectomy	5 (83.3)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No therapy	31 (57.4)	0 (0.0)	22 (40.7)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
All	125 (56.6)	33 (14.9)	39 (17.7)	16 (7.2)	4 (1.8)	4 (1.8)	0 (0.0)

emphasizes that since second line treatment options in ITP are several, they are often administered in a non-standardized way. Effects and toxicity of more second line ITP treatment deserve to be studied prospectively and with longer follow-up.

Conflict of interest disclosure

H Frederiksen has participated in the advisory board for Novartis and received research funding from Novartis. W Ghanima has participated in the advisory board for Amgen and received honoraria from Novartis and Amgen.

References

[1] Neunert C, Lim W, Crowther M, Cohen A, Solberg Jr L, Crowther MA. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117(16):4190–207.
[2] Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115(2):168–86.
[3] 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(4):1165–9.
[4] Godeau B, Chevret S, Varet B, Lefrere F, Zini JM, Bassompierre F, 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(9300):23–9.
[5] Gudbrandsdottir S, Birgens HS, Frederiksen H, Jensen BA, Jensen MK, Kjeldsen L, et al. Rituximab and dexamethasone vs dexamethasone monotherapy in newly diagnosed patients with primary immune thrombocytopenia. Blood 2013;121(11):1976–81.
[6] Mazzucconi MG, Francesconi M, Fidani P, Di NG, Gandolfo GM, Afeltra A, et al. Treatment of idiopathic thrombocytopenic purpura (ITP): results of a multicentric protocol. Haematologica 1985;70(4):329–36.
[7] Wei Y, Ji XB, Wang YW, Wang JX, Yang EQ, Wang ZC, et al. High-dose dexamethasone vs prednisone for treatment of adult immune thrombocytopenia: a prospective multicenter randomized trial. Blood 2016;127(3):296–302.
[8] Frederiksen H, Maegbaek ML, Norgaard M. Twenty-year mortality of adult patients with primary immune thrombocytopenia: a Danish population-based cohort study. Br J Haematol 2014;166(2):260–7.
[9] Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015;7:449–90.
[10] Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009;113(11):2386–93.

Henrik Frederiksen
Department of Haematology, Odense University Hospital, Odense, Denmark
Corresponding author at: Department of Haematology, Odense University Hospital, Sdr Boulevard 29, DK-5000 Odense C, Denmark.
E-mail address: hef@dadlnet.dk.

Waleed Ghanima
Department of Haematology, Østfold University Hospital Trust, Kalnes, Norway
Institute of Clinical Medicine, University of Oslo, Oslo, Norway

4 September 2016