Systematic Review and Meta-Analysis

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Immunomodulatory treatments for persistent and chronic immune thrombocytopenic purpura

A PRISMA-compliant systematic review and meta-analysis of 28 studies

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Abstract

Background Corticosteroid sparing is required in 15% to 40% of adults with persistent or chronic primary immune thrombocytopenic purpura (ITP). Herein, the efficacy of immunomodulatory drugs (dapsone, interferon alpha, danazol, and hydroxychloroquine as second-third-line therapies in ITP is investigated.

Methods MEDLINE was searched for studies that included patients with persistent or chronic primary ITP and published before the end of December 2014. Two investigators independently extracted data regarding study design, patient characteristics, dosage schedule, time to response, and occurrence of adverse events. The pooled overall response rate (ORR; platelet count $>30\times10^9\,L^{-1}$) and the complete response rate (CRR; platelet count $>100\times10^9\,L^{-1}$) were evaluated to determine drug efficacy by calculating weighted mean proportion using a fixed or random-effects model according to heterogeneity ($I^2>50\%$). The study was performed following the MOOSE and PRISMA guidelines.

Results A total of 28 studies (415 patients) were included (dapsone: k = 7 studies, n = 80; danazol: k = 12, n = 224; interferon alpha: k = 8, n = 83; hydroxychloroquine: k = 1, n = 28). The mean patient age was 50 years (female sex 70%, splenectomy 47%). The ORR and CRR were 55% (95% CI: 44%–66%, $I^2=0\%$) and 21% (95% CI: 13%–31%, $I^2=0\%$), respectively, for dapsone; 42% (95% CI: 22%–65%, $I^2=63\%$) and 18% (95% CI: 10%–29%, $I^2=9\%$), respectively, for interferon alpha; and 58% (95% CI: 42%–72%, $I^2=67\%$) and 29% (95% CI: 19%–42%, $I^2=63\%$), respectively, for danazol. The ORR was 50% (95% CI: 32%–67%) for hydroxychloroquine (data not available for CRR). Meta-regression analysis found a correlation between the ORR for interferon alpha and the splenectomized status of the patient ($P=.02$) and between the CRR for danazol and disease duration ($P<.001$). In total, 73%, 51%, 30%, and 0% of patients who received danazol, dapsone, interferon alpha, and hydroxychloroquine experienced side effects, respectively.

Conclusion The ORR was equivalent for hydroxychloroquine, danazol, and dapsone in ITP. Regarding their low CRR, patients at high risk of infection or at low risk of bleeding should benefit from these treatments. Thanks to their best efficacy and safety profiles, dapsone and hydroxychloroquine in patients with antinuclear antibodies should be preferred over danazol and interferon alpha.

Abbreviations: ACR = American College of Rheumatology, CI = confidence interval, CRR = complete response rate, ITP = immune thrombocytopenic purpura, MOOSE = Meta-Analysis of Observational Studies in Epidemiology, ORR = overall response rate, PC = platelet count, PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses, PRR = partial response rate, TPO = thrombopoietin.

Keywords: danazol, dapsone, efficacy, hydroxychloroquine, immune thrombocytopenia, interferon alpha, meta-analysis, safety

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1. Introduction

Primary immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by thrombocytopenia (platelet count [PC] $<100\times10^9\,L^{-1}$) with or without bleeding events. No clinical or laboratory parameter enables certain diagnosis, which is arrived at after ruling out other causes of thrombocytopenia. ITP is rare; the estimated incidence is between 1.6 and 3.9/100,000 adults/y and the prevalence is approximately 50/100,000 adults, especially women and elderly patients.[1,2] ITP is considered refractory in cases of splenectomy failure.[3] Treatment is warranted only for patients with PC below $30\times10^9\,L^{-1}$ or at risk of bleeding. Corticosteroids are the first-line treatment for all patients, and in association with intravenous immunoglobulin or anti-D immunoglobulin according to the risk of bleeding.[3] The initial response rate is approximately 80%, but less than 50% of patients maintain normal PC after steroid discontinuation.[4]

In cases of corticosteroid dependence, splenectomy remains a second-line treatment that is usually delayed until 12 months of disease due to the possible spontaneous recovery of ITP and the

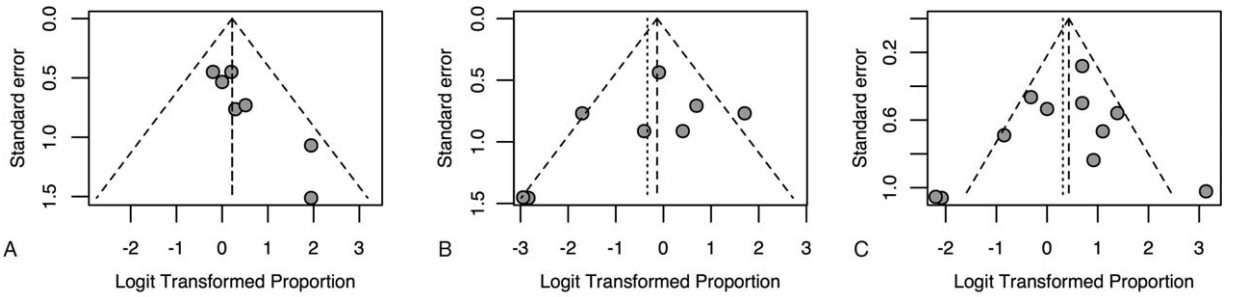


Figure 1. Study of publication bias: funnel plot of primary efficacy outcome (ORR) for dapsone (A), alpha interferon (B), and danazol (C). The visual inspection of the funnel plots retrieved no publication bias. ORR = overall response rate.

risk of complications associated with splenectomy. Following this surgical procedure the overall response rate (ORR) is approximately 60% to 80%, and at long-term follow-up, 2/3 of patients demonstrate sustainable responses. Nevertheless, 15% to 40% of patients remain refractory or experience relapse,[5,6] need other second-line treatments as well as the importance of third-line treatments. To maintain safe PC in advance of splenectomy, or in cases of relapse after splenectomy, numerous studies have assessed the efficacy of immunomodulatory treatments such as dapsone, interferon alpha, danazol, and hydroxychloroquine in persistent or chronic ITP, including post-splenectomy relapsing ITP.[7–9] New treatments such as thrombopoietin (TPO) receptor agonists are recommended after splenectomy, or in place of splenectomy if contraindicated or unsuitable. The superiority of other therapeutic options (dapsone, interferon alpha, danazol, and hydroxychloroquine) is difficult to establish because the efficacy and safety of these treatments have not been compared in a randomized controlled trial.[3,4]

This systematic review and meta-analysis aim to assess the efficacy of different immunomodulatory treatments in adults with persistent or chronic ITP.

Table 1

Characteristics of the 28 studies included in the present systematic review.

Study (first author, year of publication)	Prospective series	Consecutive series	Randomized trial	Patient reclassification
Durand, 1991	+	–	–	+
Godeau, 1993	–	–	–	+
Linares, 1994	–	–	–	+
Hernandez, 1995	+	–	–	+
Radaelli, 1999	–	–	–	+
Dutta, 2001	+	–	–	+
Zaja, 2012	–	+	–	–
Bellucci, 1989	–	–	–	+
Proctor, 1991	–	–	–	+
Chistolini, 1992	–	–	–	–
Iannaccaro, 1992	–	–	–	+
Ishii, 1992	–	–	–	+
Hudson, 1992	–	–	–	+
Dubbeld, 1994	+	–	–	+
Viannelly, 1998	–	–	–	–
Ahn, 1983	+	–	–	+
McVerry, 1985	–	–	–	–
Buelly, 1985	–	–	–	–
Almagro, 1985	–	–	–	–
Femand, 1985	–	–	–	+
Ambriz, 1986	+	–	–	+
Mazzuconi, 1987	–	–	–	+
Ahn, 1987	–	–	–	+
Fenaux, 1990	–	–	–	+
Edelmann, 1991	–	–	–	+
Kondo, 1992	–	–	–	+
Maloisel, 2004	–	+	–	–
Khellaf, 2014	–	–	–	–

2. Methods

The MOOSE (Meta-Analysis of Observational Studies in Epidemiology) and PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines were followed during all stages of design, implementation, and reporting of this meta-analysis.[10,11] All relevant published studies that described second-line treatment in primary persistent or chronic ITP were identified. The selection criteria were determined before data collection.

The meta-analysis was performed according to a prospectively developed protocol (available upon request from the corresponding author), which prespecified the research objective, the search strategy, the study eligibility criteria, and the methods of data extraction and statistical analysis. All subgroup variables were defined before analysis.

An exhaustive literature search was performed in the MEDLINE and Cochrane Library electronic databases for records that had been published before the end of December 2014, using the following keywords: immune thrombocytopenia, ITP, idiopathic thrombocytopenia, and idiopathic thrombocytopenic purpura. These Medical Subject Heading terms were combined with each of the following: dapsone, interferon alpha, danazol, and hydroxychloroquine. The searches were restricted to articles published in English or French language. To identify additional references, references cited by relevant articles were manually checked, and Google Scholar and conference proceedings in the fields of hematology and internal medicine were also consulted.

With regard to the design of the present study (use of published pooled data), ethical approval was not necessary.

2.1. Study selection

All studies describing second-line treatments for chronic or persistent primary ITP in adults (≥18 years) were included. Primary ITP was defined by exclusion of the other causes of thrombocytopenia (solid tumor, lymphoma, drug-induced ITP, viral infections, systemic diseases such as lupus, and primary immunodeficiency). ITP was classified as persistent (≥3 months duration) or chronic (≥1 year duration) according to international

Table 2

Treatment exposure and characteristics of patients included in the present systematic review.

Author, y (study reference)	Drug	P/C	N	Mean age, y	Male sex, %	Mean DD, mo	Mean initial PC, G/L	Splenectomy, %	Dose	Concomitant therapy	Previous treatment
Durand, 1991[15]	Dapsone	P	1	87	0	6	23	0	75 mg/d during 2–48 mo	No	1 P, 1 VBL, 1 IVIg, 1 Dnz
	Dapsone	C	2	70	50	54	39	0		No	1 P, 1 Dnz, 2 IVIg, 1 colchicine, 1 VBL
Godeau, 1993[16]	Dapsone	P	8	40	12	8	16	0	100 mg/day	2 Dnz	8 Cs, 3 Dnz, 4 IVIg, 1 VCR
	Dapsone	C	12	49	33	80	22	3		2 Dnz, 3 steroids	11 P, 7 IVIg, 3 VBL, 8 Dnz, 3 CYC, 4 Aza, 2 VCR, 2 IFN, 2 CsA, 1 ascorbic acid
Linares, 1994[17]	Dapsone	C	7	49	29	85	17	2	100 mg/day	NA	NA
Hernandez, 1995[18]	Dapsone	C	14	57	29	49	23	3	100 mg/day	No	14 P, 6 Aza
Radaelli, 1999[19]	Dapsone	C	8	63	38	147	18	6	75–100 mg/day	2 Steroids	8 deltacorten, 7 Dnz, 5 IVIg, 1 vindesine, 2 anti-D, 2 CYC, 3 VBL, 1 Aza, 1 IFN
Dutta, 2001[20]	Dapsone	P	1	18	0	9	60	0	100 mg/day	No	P
		C	7	30	43	58	25	2		No	7 P, 4 anti-D, 2 VCR, 1 colchicine, 2 Dnz, 1 Aza, 1 ascorbic acid
Zaja, 2012[21]	Dapsone	P/C	20	51*	45	46*	19*	5	50 mg/d during first wk then 100 mg/d for 2 mo	Steroids on maintenance therapy	20 Cs, 20 RTX, 6 Aza and or CsA, 1 Dnz
Bellucci, 1989[22]	Interferon alpha	C	9	55	11	NA	27	NA	9 MU/wk for 4 wks	NA	NA
Proctor, 1991[23]	Interferon alpha	NA	13	50	23	NA	13	8	9 MU/wk for 4 wks	3 Steroids on maintenance therapy	12 P, 4 IVIg, 1 Dp, 1 Dnz, 1 VCR, 1 Aza, 1 chlorambucil
Chistolini, 1992[24]	Interferon alpha	C	13	60*	23	84*	17*	3	1 MU/d for first wk then 2 MU/day for second wk then 9 MU/wk until 12 wks	NA	13 Cs
Iannaccaro, 1992[25]	Interferon alpha	NA	8	43	25	NA	36	1	9 MU/wk for 4 wks	No	7 P, 8 IVIg, 1 Dnz
Ishii, 1992[26]	Interferon alpha	C	5	49	20	122	25	3	18 MU/wk for 4 wks	4 Steroids	5 P, 3 Dnz, 3 cepharanthin, 2 colchicine, 3 ascorbic acid, 4 neurotropin 5, 2 CsA, 4 VA slow I, 3 IVIg
Hudson, 1992[27]	Interferon alpha	NA	5	57	40	NA	22	2	9 MU/wk for 4 wks then 3 MU 5 times/wk	NA	5 Cs, 1 Aza, 1 IVIg
Dubbeld, 1994[28]	Interferon alpha	P	1	65	0	8	NA	1	9 MU/wk for 4 wks	No	Cs
		C	20	54	45	84	NA	20		No	20 Cs, 8 Aza, 4 VCR, 9 Dnz, 11 IVIg, 11 ascorbic acid, 1 CYC, 1 colchicine
Vianelly, 1998[29]	Interferon alpha	C	9	55*	33	37*	25	4	9 MU/wk for 5 wks	No	9 Cs, 8 Aza, 2 IVIg
Ahn, 1983[30]	Danazol	C	20	58	40	97	20	13	400–800 mg/day	Drugs were modified when improvement was noted	20 Cs, 2 IVIg, 16 VA, 6 Aza, 3 CYC, 16 colchicine, 6 plasmapheresis
McVerry, 1985[31]	Danazol	P	1	78	0	7	PC <50†	0	400 mg/day for 1 mo then 600 mg/day for 2 mo	NA	Cs, VCR
		C	9	59	11	82		6		NA	9 Cs, 4 Aza, 2 VCR
Buelli, 1985[32]	Danazol	NA	14	51	36	NA	43	6	600 mg/day for 2 mo	Steroids discontinuation during treatment	P
Almagro, 1985[33]	Danazol	NA	9	NA	11	NA	NA	NA	400–800 mg/day for 8 wks	NA	NA
Fermand, 1985[34]	Danazol	P	7	41	14	8	NA	0	600 mg/day	1 P	7 P, 1 IVIg
		C	17	51	23	54	NA	10		5 P	17 P, 11 VCR, 10 IVIg, 4 CYC, 7 Aza
Ambriz, 1986[35]	Danazol	C	24	27	0	80	24	24	600 mg/d for 4 mo and decreased after 4 mo to 100–200 mg/day	8 Low-dose prednisone, other drugs were modified promptly when improvement was noted	24 P, 12 Aza, 8 VA, 17 colchicine, 2 accessory spleen surgery, 6 CsA, 1 plasmapheresis

(*continued*)

Table 2
(continued).

Author, y (study reference)	Drug	P/C	N	Mean age, y	Male sex, %	Mean DD, mo	Mean initial PC, G/L	Splenectomy, %	Dose	Concomitant therapy	Previous treatment
Mazzuconi, 1987[36]	Danazol	P/C	10	58*	60	22*	24	1	600 mg/d for 3 mo	8 P (0.05–0.2 mg/kg/d)	10 P
Ahn, 1987[37]	Danazol	C	18	61	22	9	NA	10	400–800 mg/day	No	18 P, 2 IVig, 1 délatestryl, 8 VA, 7 colchicine, 2 Aza, 2 CYC
Fenaux, 1990[38]	Danazol	P	1	68	0	8	20	1	600 mg/d at least 2 mo	No	IVig, Aza
		C	18	55	50	55	24	11		No	16 P, 1 IVig, 3 VCR, 13 Aza
Edelmann, 1991[39]	Danazol	P	1	55	100	4	9	0	800 mg/day for at least 3 mo	Steroids	P, VCR, colchicine
		C	6	66	33	87	22	0			6 P, 2 VCR, 1 colchicine, 3 Aza
Kondo, 1992[40]	Danazol	P	3	63	33	6	NA	0	Low dose (<100 mg/day), medium (100–400 mg/day), high >400 mg/day	2 Steroids	3 P, 1 IVig
		C	9	50	22	45	NA	1		2 Steroids	6 P, 1 IVig, 1 Aza
Maloisel, 2004[8]	Danazol	P/C	57	54*	40	24*	21*	27	600 mg/day	No	53 Cs, 21 IVig, 4 IS, 4 chemotherapy
Khellaf, 2014[41]	HCQ	NA	28	37	25	NA	14	0	200–600 mg/day	NA	NA

anti-D = anti-D immunoglobulin, Aza = azathioprine, Cs = corticosteroids, CsA = cyclosporine, CYC = cyclophosphamide, DD = disease duration, Dexa = dexamethasone, Dnz = danazol, Dp = dapsone, IFN = interferon, IVig = intravenous immunoglobulin, P = prednisone, PC = platelet count, P/C = persistent/chronic, HCQ = hydroxychloroquine, IS = immunosuppressive agents, mo = months, MP = methylprednisolone, MMF = mycophenolate mofetil, MU = million units, N = number of patients included, NA = not available, VA = vinca alkaloids, VBL = vinblastine, VCR = vincristine, VLP = vincristine loaded platelet, RTX = rituximab, S = splenectomy, T = treatment, wks = weeks, y = years.

* Median.

† Except 1 patient PC 30–70 G/L

guidelines.[3] Studies concerning children were excluded. Articles describing fewer than 5 patients were not selected due to the risk of bias. When papers were identified from the same series, only the latest or most informative studies were included.

2.2. Data extraction and quality assessment

Data from the eligible studies were independently extracted by 2 authors (EW and RF). In case of discrepancy, a consensus was reached. The extracted study characteristics included the year of publication, design (prospective or retrospective), patient characteristics, median time of disease duration, number of splenectomized patients, and prior treatments. Treatments (dosage schedule of treatments of interest, and concomitant treatments), mean PC before the treatment of interest, maximal PC, duration of response, mean follow-up, side effects, and adverse events were collected.

PC responses were analyzed as defined by the international consensus: PC $>100\times10^9$ L^{-1} for a complete response rate (CRR), PC $>30\times10^9$ L^{-1} for partial response rate (PRR), and no response when PC was $<30\times10^9$ L^{-1}.[4] For each of the studies, the numbers of patients with ORR, CRR, and PRR were extracted.

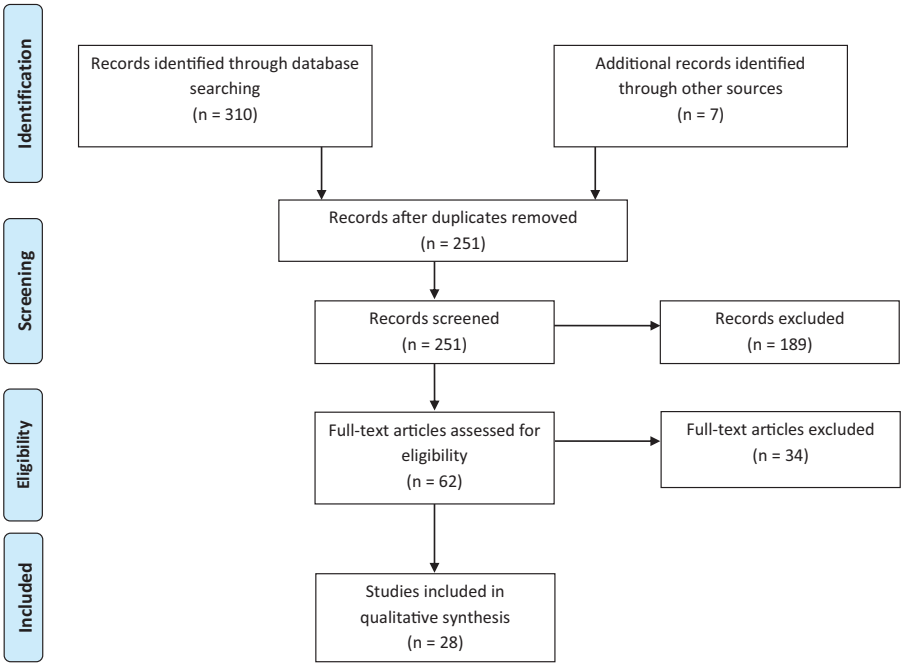
2.3. Data synthesis and analysis

The primary outcome was ORR, expressed as a mean rate, together with its 95% confidence interval (95% CI). The secondary outcomes were CRR and PRR. Treatment efficacy was estimated by calculating the weighted mean proportion with logit transformation. The response rate estimates were obtained using the fixed effects model method when heterogeneity was negligible. The percentage of variability beyond chance was estimated using the I^2 statistics.[12,13] I^2 statistics greater than 50% indicate substantial heterogeneity. To determine the expected heterogeneity, the random-effects model was used. To explain heterogeneity, the effects of covariates on the response rate were investigated using meta-regressions. The β coefficient describes the relationship between responses (dependent variable) and patient or study characteristics (independent variables). For each 1 unit increase in independent variables, the rate of response increased by β%. The risk of publication bias was determined by funnel plot.[14] All analyses were performed using R Software (R Development Core Team [2008]. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) with Package metafor (version 1.9-5).

3. Results

3.1. Study selection

A total of 310 records were identified by searching electronic database and 7 records manually. A total of 251 records were retained after removal of duplicates. After screening titles and abstracts, 189 records that were not relevant were excluded. Sixty-two full-text articles were assessed for eligibility. A total of 28 studies[8,15–41] that fulfilled the criteria were included in the meta-analysis (Flow Chart) and represented a total of 415 patients. No publication bias was suspected by visual inspection of funnel plots (Fig. 1). Six studies were prospective,[15,18,20,28,30,35] and 2 studies included consecutive series of patients.[8,21] Individual data were available for 21 studies that



included 279 patients. The quality assessment of the selected studies is detailed in Table 1.

The available patient characteristics are summarized in Table 2. The mean age was 50 years, and 60% of patients were female. Ten percent of patients had persistent ITP. The mean disease duration was 50 months (range: 8–147 months, disease duration was not detailed for 164 patients), and the mean PC before treatment was 22×10^9 L^{-1} (range: 9–60 $\times 10^9$ L^{-1}). All but 14 patients received corticosteroids as first-line therapy; 5 patients were initially managed with intravenous immunoglobulins only,[15,16,25,38] 3 did not receive previous treatment,[40] 2 were treated with other first-line therapies (splenectomy[38] or danazol and vincristine),[23] and for 4 patients the first-line therapies were not reported.[8] Of the 397 patients, 43.6% were splenectomized (data unavailable for 18 patients). Previous treatments with other immunosuppressive or immunomodulatory drugs are reported in Table 2.

3.2. Dapsone

Seven studies investigated dapsone,[15–21] and these included 80 patients (mean age 51 years, female 49%). Dapsone was administered orally with doses ranging from 75 to 100 mg daily (Table 2).

The ORR for dapsone was estimated to be 55% (95% CI: 44%–66%, $I^2 = 0\%$), CRR to be 21% (95% CI: 13%–31%, $I^2 = 0\%$) (Fig. 2), and PRR to be 38% (95% CI: 28%–50%, $I^2 = 9\%$). No significant heterogeneity was observed among outcomes. The time to response ranged from 1 to 2 months and the duration of response from 17 to 42 months (Table 3).

Thirty-nine side effects were reported in 77 patients[16–21] and were described as hemolysis without anemia, hemolytic anemia, or methemoglobinemia in 34 cases. Others side effects included nausea (n = 3), vomiting (n = 3), headache (n = 3), or hepatic cytolysis (n = 2). No deaths occurred during treatment.

3.3. Interferon alpha

Eight studies investigated interferon alpha (22–29), and these included 83 patients (mean age 54 years, female 59%) were included. Three million units were administered subcutaneously 3 times weekly during 4 to 12 weeks except in 2 studies[24,26] (Table 2).

The ORR was estimated to be 42% (95% CI: 22%–65%, $I^2 = 63\%$), CRR to be 18% (95% CI: 10%–29%, $I^2 = 9\%$) (Fig. 3), and PRR to be 37% (95% CI: 26%–49%, $I^2 = 41\%$). The time to response was not available; the duration of response ranged from 2 weeks to 8 months (Table 3). Because of the heterogeneity of

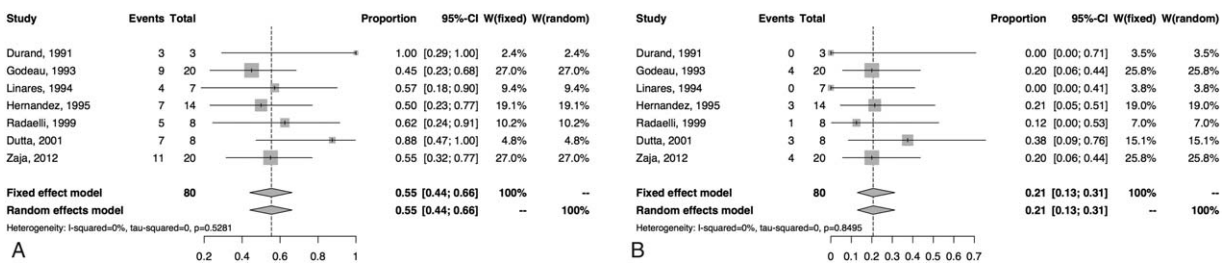


Figure 2. Forrest plots of ORR (A) and CRR (B) of dapsone estimated from 7 studies totalizing 80 patients. CRR = complete response rate, ORR = overall response rate.

Table 3

Description of the effects of immunomodulatory treatments.

Author, y (study reference)	Drug	Persistent or chronic disease	TTR/DR	Peak, G/L/TTP	Follow-up	Splenectomy among responders	Bleeding/ infections	Death	Relapse, %
Durand, 1991[15]	Dp	P/C	NA/22 mo	103/NA	NA	0	No/No	No	100 (with response at second course)
Godeau, 1993[16]	Dp	P	NA/NA	100†/NA	NA	—	NA/No	No	NA
		C	NA/NA	139†/NA	NA	1	NA/No	No	
Linares, 1994[17]	Dp	C	1–2 mo/NA	72†/NA	NA	1	NA/No	No	NA
Hernandez, 1995[18]	Dp	P/C	NA/NA	85/NA	NA	1	NA/No	No	NA
Radaelli, 1999[19]	Dp	C	NA/NA	65†/NA	NA	4	NA/No	No	NA
Dutta, 2001[20]	Dp	P	NA/NA	130†/3 wks	NA	—	NA/No	No	100 (with response at second course)
		C	NA/NA	167†/6 wks	NA	2	NA/No	No	29 (with response at second course, 2 still on treatment)
Zaja, 2012[21]	Dp	P/C	1 mo*/42 mo*	103†/NA	42* (8–56)	NA	NA/No	No	NA
Bellucci, 1989[22]	IFN	C	NA/all transient (<14 d or less)	104/13 d	NA	NA	NA/No	No	100
Proctor, 1991[23]	IFN	NA	NA/21 wks	160/38 d	NA	NA	NA/No	No	38 (with response at second course)
Chistolini, 1992[24]	IFN	C	NA/NA	NA/NA	NA	NA	NA/No	No	15 (at 2 and 4 mo)
Iannaccaro, 1992[25]	IFN	NA	NA/8 mo	65†/NA	NA	—	NA/NA	No	100
Ishii, 1992[26]	IFN	C	NA/24 d	97/28 d	NA	2	4 Improvement/NA	No	40 (after the second peak at 5 wks)
Hudson, 1992[27]	IFN	NA	NA/NA	NA/NA	NA	1	NA/No	No	NA
Dubbeld, 1994[28]	IFN	P	—	NA/NA	NA	—	NA/No	No	—
		C	NA/8 wks	74/5 wks	NA	10	NA/No	No	50
Vianelly, 1998[29]	IFN	C	NA/NA	28†/NA	NA	—	4 Persistent bleeding/No	No	100
Ahn, 1983[30]	Dnz	C	NA/7 mo (3 CR: response <1 mo)	160†/NA	NA	10	NA/No	No	NA
McVerry, 1985[31]	Dnz	P/C	NA/NA	NA/NA	NA	NA	NA/No	No	50
Buelli, 1985[32]	Dnz	NA	NA/4 mo	135†/NA	NA	3	NA/No	No	29
Almagro, 1985[33]	Dnz	NA	NA/NA	NA/NA	NA	NA	1 Intracranial bleeding/No	No	NA
Fermand, 1985[34]	Dnz	P/C	NA/NA	NA/NA	NA	7	NA/No	No	NA
Ambriz, 1986[35]	Dnz	C	NA/NA	170†/NA	NA	23	No/No	No	NA
Mazzuconi, 1987[36]	Dnz	P/C	NA/NA	NA/NA	NA	NA	NA/No	No	—
Ahn, 1987[37]	Dnz	C	3/14 mo	NA/NA	NA	6	All improved/No	No	NA
Fenaux, 1990[38]	Dnz	P	Within 2 mo of onset/8 mo	11	NA	—	NA/No	NA	0
		C		55/NA		5		1 (4 mo after withdrawal)	28
Edelmann, 1991[39]	Dnz	P	NA/NA	65/NA	40	0	NA/No	No	NA
		C	NA/(3, 44, 51 and transient)	131/NA	29 mo (8,5–50)	0	NA/No	No	100
Kondo, 1992[40]	Dnz	P	NA/NA	NA/NA	NA	0	NA/NA	NA	NA
		C	NA/NA	NA/NA	NA	1	NA/NA	NA	NA

(*continued*)

Table 3
(continued).

Author, y (study reference)	Drug	Persistent or chronic disease	TTR/DR	Peak, G/L/TTP	Follow-up	Splenectomy among responders	Bleeding/ infections	Death	Relapse, %
Maloisel, 2004[8]	Dnz	P/C	3 mo*/119 mo*	142†/NA	70*	17	NA/No	9 (2 due to ITP, 3 cancer; 4 unknown)	21
Khellaf, 2014[41]	HCQ	P/C	NA/NA	NA/NA	NA	0	NA/No	No	NA

Aza = azathioprine, C = corticosteroid, CR = complete response, CsA = cyclosporine, CYC = cyclophosphamide, d = day, Dnz = danazol, Dp = dapsone, DR = duration of response, IFN = interferon, MMF = mycophenolate mofetil, mo = months, N = number of patients, NA = not available, NR = no response, P = prednisone, PC = platelet count, P/C = persistent/chronic, PR = partial response, OR = overall response, RTX = rituximab, TTP = time to peak response, TTR = time to response, VA = vinca alkaloids, VBL = vinblastine, VCR = vincristine, wks = weeks, y = year.
* Median.
† PC after treatment.

treatment effect for ORR, a meta-regression analysis was performed to predict the response according to patient characteristics. Splenectomy was correlated with better ORR (k = 6, β coefficient = 1.31, $P = .02$) in meta-regression.

Side effects consisted of flulike syndrome in 25 patients and neutropenia in 1 case. No cases of infection or death were described during the follow-up period.

3.4. Danazol

Twelve studies investigated danazol,[8,30–40] and these included 224 patients (mean age 56 years, female 56%). Danazol was administered from 400 to 800 mg daily for at least 2 months. Only 1 study used a low dose of 100 mg daily in 1 group of patients[40] (Table 2).

The ORR of danazol was estimated to be 58% (95% CI: 42%–72%, $I^2 = 67\%$), CRR to be 29% (95% CI: 19%–42%, $I^2 = 63\%$) (Fig. 4), and PRR to be 30% (95% CI: 20%–43%, $I^2 = 58\%$), with significant heterogeneity for all outcomes. The time to response varied from 2 to 3 months, with a response duration ranging from 4 to 119 months (Table 3). The number of previous immunosuppressive drugs used and disease duration were associated with better CRR (k = 7, β coefficient = 0.12, $P = .02$; and k = 9, β coefficient = 0.005, $P < .001$, respectively). Only disease duration was correlated with CRR in multivariable analysis. Younger age and disease duration were weakly associated with better ORR (k = 10, β coefficient = −0.01, $P = .05$; and k = 9, β coefficient = 0.005, $P = .05$, respectively) in multivariable analysis.

Ten (5%) patients died of bleeding (n = 2), cancer (n = 3), and for unknown reasons (n = 5) during the follow-up. Fifteen patients experienced side effects that led to danazol withdrawal. Among 135 patients (with individual data available), 99 (74%) side effects included amenorrhea (n = 29), liver test abnormalities (n = 25), weight gain (n = 7), acne (n = 4), headaches (n = 2), masculinization (n = 2), or intracranial hypertension (n = 1).

3.5. Hydroxychloroquine

One study investigated hydroxychloroquine (41), and it included 28 patients (mean age 37 years, female 67%) who were positive for antinuclear antibodies but without American College of Rheumatology (ACR) criteria for systemic lupus erythematosus. Hydroxychloroquine was administered at 200 to 600 mg daily. The time to response was 4 to 6 months, and the duration of response was 5 years. The ORR was estimated to be at 50% (95% CI: 8%–59%). No retinal deposits or other side effects were observed.

4. Discussion

This is the first meta-analysis evaluating the efficacy of immunomodulatory drugs as second-line treatments for adults with persistent and chronic ITP. This question is challenging because the risk of bleeding is difficult to determine in patients with low PC, and treatments may have side effects that outweigh the risk of bleeding.[42] Recommendations and evidence guiding the choice of the treatment in adults with persistent or chronic ITP are lacking,[3] with the exception of rituximab and TPO receptor agonists.[43–45] Danazol, hydroxychloroquine, and dapsone had similar efficacy in the present meta-analysis, and these were higher and more sustained compared with those of interferon alpha. Taken together, the ORR ranged from 42% to 58% for immunomodulatory drugs, and this effect mainly corresponded to a PRR in 1/3 of exposed patients. These drugs

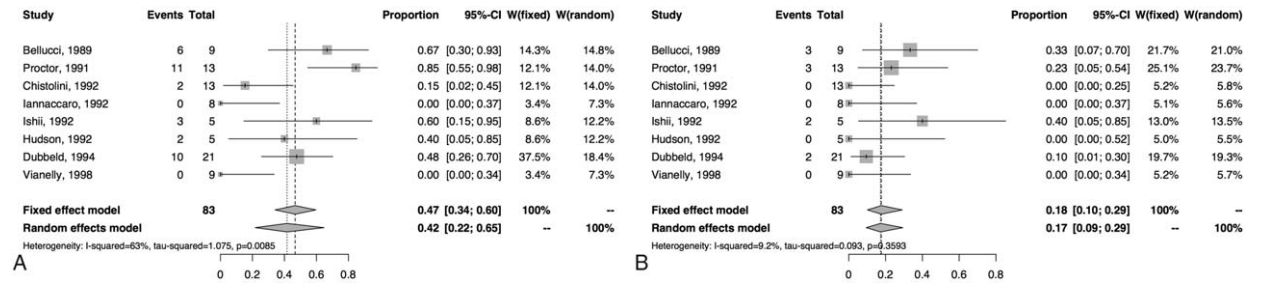


Figure 3. Forrest plots of ORR (A) and CRR (B) of interferon alpha estimated from 8 studies totalizing 83 patients. CRR = complete response rate, ORR = overall response rate.

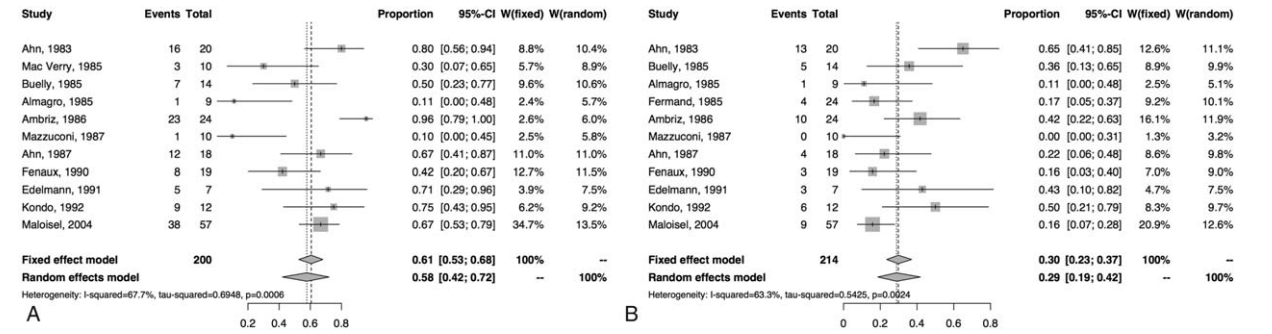


Figure 4. Forrest plots of ORR (A) and CRR (B) of danazol from 11 studies totalizing 214 patients. CRR = complete response rate, ORR = overall response rate.

are a less expensive alternative to rituximab and TPO-antagonists with a monthly cost less than $100, except for interferon alpha.[46] They may be preferred, especially in case of fear of infections related to immunosuppression associated with rituximab. However, with regard to their times of response, danazol, dapsone, and hydroxychloroquine should not be used in life-threatening cases and should be coadministrated to a transient course of corticosteroids.[46]

Given their similar efficacies, the choice of immunomodulatory treatment should be based on expected side effects. Thus, with regard to cost and the related side effects, interferon alpha should be avoided in the modern era of ITP treatment. The use of danazol is compromised by the occurrence of side effects in 3/4 of patients, mainly amenorrhea, skin reaction, weight gain, or liver abnormalities, which may lead to undesirable treatment cessation. Moreover, 5% of patients died during follow-up after treatment with danazol. Contrary to what is described in cases reports,[47,48] no case of thrombosis or liver cancer was identified in the present meta-analysis. Furthermore, the risk of virilization limits its use in woman. The target population susceptible to receive danazol is older patients at low risk of cardiovascular events and hormonal-induced cancer or with suspicion of underlying myelodysplastic syndrome.[46] Side effects seemed to be less frequent with dapsone in the present study and consisted of moderate hematological events, and this therapy should be preferred in patients unsuitable for immunosuppressive drugs. Notably, no case of dapsone hypersensitivity has been reported, probably because of its rarity in patients of European ancestry.[49] Because Europeans represent the majority of published cases treated by dapsone in the present meta-analysis, we cannot exclude an overestimation of the drug safety for patients without European genetic backgrounds. Hydroxychloroquine is well tolerated and was associated with an ORR in half of patients with antinuclear antibodies but without overt systemic lupus. Hydroxychloroquine should be considered for these patients as an alternative to dapsone. However, as already discussed, it should be associated with corticosteroids during the first weeks of treatments because of its long time to response.[46]

The present meta-analysis included some limitations. First, no randomized controlled trial was included. Thus, it could not provide unbiased head-to-head comparison of treatment effects. In addition, treatment effects observed in observational studies are usually overestimated when compared with randomized trials, which may contribute to overestimation of results.[50] Therefore, results have to be confirmed by randomized trials such as that conducted in France (NCT02627417). Second, retrospective and nonconsecutive series constituted the majority of selected studies responsible for bias. Third, the results included substantial heterogeneity that was partially explained by meta-regressions. Moreover, the results of meta-regression must be viewed as exploratory and have to be confirmed by patient level analysis. Thus, in the study reported by Maloisel et al, danazol seemed more effective in patients over 45 years contrary to the results of meta-regression.[8] Given the limitations of meta-regression, the differences in design, local practices, genetic background, splenectomized status, patient characteristics, rates of nonadherence, withdrawal secondary to side effects, and administered doses might be responsible for the variations in estimated effects. Taken together, the present meta-analysis presented uncontrolled results susceptible to be influenced by bias.

5. Conclusion

The response rates were equivalent for dapsone, danazol, and hydroxychloroquine with an ORR of 50% to 60% in second-line treatment of persistent or chronic ITP. The low CRR associated

with these treatments suggests their use in patients at high risk of infection or low risk of bleeding. Regarding their efficacy and safety profiles, dapsone and hydroxychloroquine in patients with antinuclear antibodies should be preferred over danazol and interferon alpha.

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