Intravenous Rhesus Immune Globulin and Intravenous Immunoglobulin in Immune Thrombocytopenic Purpura

a report by

James Bussel,[1] **Michael D Tarantino**,[2] **Luba Nalysnyk**,[3] **Kyle Fahrbach**,[3] **Brian Sercus**,[3] **Maurice Genereux**[4] *and* **Chris Sinclair**[4]

1. Department of Pediatrics, Weill Medical College of Cornell University, New York; 2. Comprehensive Bleeding Disorders Center, University of Illinois College of Medicine; 3. United BioSource Corporation, Medford; 4. Cangene Corporation, Winnipeg

DOI: 10.17925/EOH.2007.0.0.37

Immune thrombocytopenic purpura (ITP) is an autoimmune bleeding disorder characterised by antibody-induced platelet destruction.[1,2] Intracranial haemorrhages are the most serious and life-threatening complications, with mortality of 0.2–1% in acute ITP and up to 3% per year in the chronic form.[3,4] Almost all intracranial haemorrhages occur when platelet counts (PCs) are below $20x10^9$/l, and most below $10x10^9$/l. Therefore, the goal of treatment for severe ITP at the time of diagnosis is not to achieve a normal platelet count, but rather to prevent significant bleeding events by raising PC to above 30–$50x10^9$/l. Standard treatments of ITP include glucocorticoids, intravenous immunoglobulin (IVIG) and other immunosuppressive agents, including rituximab, all of which are intended to interfere with the immune-mediated platelet destruction. Splenectomy is offered in refractory cases.[3] Since the US Food and Drug Administration (FDA) approval for use in ITP patients in 1995, IV rhesus immune globulin (RhIG) (WinRho® SDF, Cangene Corporation, Winnipeg, Canada) has been increasingly offered as a front-line treatment for ITP because it is effective, safe, has a much shorter infusion time and is less expensive than IVIG.[6] It is licensed in the US, Canada, Europe and other countries for the treatment of acute or chronic ITP in paediatric patients, chronic ITP in adults and ITP secondary to HIV.[7] The aim of this systematic review and analysis is to examine the efficacy and safety of IV RhIG in adults and children with acute or chronic ITP relative to the efficacy and safety of IVIG.

Methods

Our procedures for this review followed established best methods for the evolving science of systematic review research.[8–10] A protocol was written prospectively, which stated the objectives, search criteria, study selection criteria, data elements of interest and plans for analysis.

Data Sources

English-language literature was searched from January 1985 to March 2005. A broad search of the literature was performed, including both electronic and manual components. The Medical Literature Analysis and Retrieval System Online (MEDLINE), the Excerpta Medical Database (EMBASE) and the Current Contents™ database were searched for all relevant articles. The following search strategy was used:

1. Purpura, thrombocytopenic, idiopathic (MESH), 'ITP', 'immune thrombocytopenic purpura' or 'idiopathic thrombocytopenic purpura';
2. Rho(D) immune globulin (MESH) or IGIV (MESH) or gamma-globulin (MESH) or 'Winrho' or 'RhoGAM' or 'IG' or 'IV RhIG antibody'; or
3. Numbers 1 and 2.

A manual reference check of all accepted publications and recent review articles was performed to supplement the above electronic searches. In addition to the published literature, abstracts from the 2001–2004 American Society of Hematology (ASH) conference proceedings were searched for studies that appeared to meet eligibility criteria for inclusion in this review, but were not yet published as complete reports. Study eligibility requirements were the same for abstracts and full publications.

Study Selection

Two reviewers had to agree on all acceptances or rejections and if necessary were reconciled by consensus. A study had to satisfy the following criteria:

- at least 10 patients with ITP, either acute or chronic, per treatment group;
- at least 50% of patients must have primary or HIV-related ITP, and at least 50% with intact spleens;
- treatment with IV RhIG or IVIG with clinical outcomes reported separately for each treatment; and
- reporting efficacy (response rate, time to response and/or duration of response) and/or safety outcomes.

All study designs were accepted, including randomised controlled trials (RCTs), prospective and retrospective non-randomised controlled trials (nRCTs) and uncontrolled case series (UCS). In cases where multiple publications of the same patient population were identified, the study reporting on the larger number of patients was used to avoid double-counting patients. Studies published prior to 1985, non-English-language articles, case reports of <10 patients, studies in patients with prior splenectomy and studies of neonates were excluded.

Database Development

Protocol-defined data elements from each eligible study were extracted by one researcher onto a data extraction form (DEF), and all elements were reviewed and agreed upon by a second investigator, checking all extracted data against the original report. Differences were resolved by consensus prior to data entry. Specific IG names for IV RhIG (e.g. WinRho) and IVIG (e.g. Sandoglobulin) and their dosing information were captured if reported. Dosing regimens were categorised as low (IV RhIG <50μg/kg and IVIG <1g/kg), conventional (IV RhIG=50μg/kg and IVIG=1g/kg) and high (IV RhIG >50μg/kg and IVIG >1g/kg). We used the following definitions and conventions for managing highly variable response measures in these studies.

- 'Overall response' includes all studies regardless of response timing or definition – in studies reporting multiple response thresholds, the highest response rate was used.

Table 1: Baseline Patient Characteristics

Characteristics		IV RhIG			IVIG		
		t	n	% or mean	t	n	% or mean
Total patients evaluated		36	1,027	100	85	2,063	100
Gender	Males	22	362/648	56	60	642/1,345	48
	Females	22	283/648	44	60	703/1,345	52
Age of population	Children (<16 years)	32	583/869	67	81	1,257/1,845	68
	Adults	32	283/869	33	81	588/1,845	32
Mean age range (years)		22	387	3–69	58	1,347	3–65
ITP duration (range, months)		10	161	29 (1–124)	23	428	21 (0–101)
ITP type	Acute	30	315/839	38	73	1,040/1,621	64
	Chronic	30	517/839	62	73	552/1,621	34
ITP cause	Primary	29	645/811	80	79	1,728/1,854	93
	HIV-related	30	157/909	17	79	77/1,854	4
	Other secondary	29	6/811	1	79	19/1,854	1
Patients Rh+			29	723/737	98	4	100/114 88
Prior ITP treatments	Naïve	19	224/367	61	45	832/1,150	72
	Steroids	20	151/393	38	51	297/1,194	25
	IVIG	18	60/358	17	37	4/969	0.4
	IV RhIG	14	7/297	2	31	2/873	0.2
	Splenectomy	28	18/737	2	52	79/1,195	7
Baseline platelet count ($x10^9$/l)	Mean (range of means)	10	184	15 (9–31)	38	794	16 (4–45)
	Median (range of medians)	16	328	13 (5–34)	34	656	13 (2–40)

t = number of treatment groups; n = number of patients with characteristic/all patients evaluated; IV = intravenous; RhIG = rhesus immune globulin; IVIG = intravenous immunoglobulin, ITP = immune thrombocytopenic purpura.

- 'Response within 24 hours' includes any response reported within that time interval.
- 'Response within ~7 days' includes studies reporting response in the interval between five and 10 days of IG treatment. We used the definitions of authors of acute and chronic ITP, which were commonly defined as acute-onset, short-term (<6 months) for acute ITP and thrombocytopenia persisting for >6 months for chronic ITP.

Data Synthesis and Analysis

Basic descriptive statistics were applied to summarise study, patient and treatment characteristics. The response outcomes (overall response, 24-hour response, seven-day response, time to response, duration of response, time to peak PC and maximum platelet increase) and selected safety outcomes (headache, fever, chills, vomiting, aseptic meningitis, bleeding, dyspnoea, asthaenia and haemoglobin change) for patients treated with IV RhIG and IVIG were first estimated using pooled analyses (as weighted means for continuous variables and as proportions for binary outcomes). In addition, response rates were analysed using random-effects model (REM) meta-analyses.[11] The REM meta-analyses weighted response rates by a combination of study sample size and between-study variation. The higher the between-study variation (i.e. the more heterogeneous the study results), the less impact that study sample had in weighting the studies in the analysis. Studies not defining response or not specifying time interval of response were included only in the 'overall response' analysis. Subgroup analyses for efficacy outcomes were performed for patients with acute versus chronic ITP. Heterogeneity in all meta-analyses was examined using Cochran's Q statistic. No formal meta-analytical comparison between IV RhIG and IVIG treatments was performed due to lack of head-to-head studies and variability of outcome reporting. For safety analyses, zeros were imputed for mortality in studies reporting safety outcomes without any mention of patient deaths. All calculations were performed using SAS® software version 8.1 and SPSS® software version 13.0. The three randomised trials directly comparing IV RhIG versus IVIG are described separately in the results section.

Results

Studies

The initial search yielded 1,014 citations, of which the vast majority were excluded at abstract level for obvious rejection reasons (e.g. reviews, not ITP population, no IV RhIG or IVIG treatments). Full publications were retrieved for 280 abstracts for further review. Of these, 181 publications were rejected for reasons such as review article, fewer than 10 patients per treatment group and non-English language. Ninety-nine publications met all eligibility criteria for inclusion in the database. During screening and extraction, linkages were identified among the accepted studies. Linked studies were those in which the same patient population was reported, in part or in total, in more than one publication. The study with the most complete data was designated the 'parent' study, and the other related papers were designated 'kins'. Data elements were extracted from the parent studies and supplemented by information presented in kin studies when appropriate. After determining these kin relationships, the final database of accepted studies consisted of 92 parent studies with seven linked (kin) studies. Of the 92 primary accepted studies, three single-arm studies were excluded from all analyses as they evaluated combination treatments of IVIG[12,13] and IV RhIG[14] with steroids. The first study treatment consisted of IV high-dose methylprednisolone (20mg/kg in 30 minutes) followed by IV gamma globulin (Gamimune-N, 1g/kg over five hours).[12] In the second study the patients previously received prednisone 20–40mg/day, and the steroid therapy continued during the IVIG treatment.[13] In the third study, patients received prednisone at 1mg/kg/day as a single dose for 14 days and then diminished every three days by half the previous dose until reaching a dose of 5mg/day for three days, and then discontinued.[14] This review focused primarily on monotherapy with IV RhIG and IVIG, although patients might have been allowed to receive steroids or other treatments during the study.

The final analysable data set consisted of 89 primary studies, of which 77 were full publications and 12 were abstracts. Not surprisingly, there were more than twice as many studies evaluating IVIG as there were evaluating IV RhIG. Of the total 3,127 patients evaluated, 67% (n=2,096) were treated with IVIG, and 33% (n=1,031) with IV RhIG. WinRho was specifically identified as the IV RhIG used in 60% of all IV RhIG studies evaluating at least 72% of all IV RhIG-treated patients. Other IV RhIG brands used were Partogamma, Rhesuman, Rhogam and HypRho-D. Of the 50 studies published between 1995 and 2005, 38 were full publications and 12 were meeting abstracts. The IVIG product used was not specified in 20 studies, and in nine studies patients were treated with various IVIG products. In studies reporting this information, Sandoglobulin was most commonly used (k=15). Other IVIG products included Venoglobulin, Venogamma, Polygam, Gamimune, Gammagard and Gamunex. Of the 89 studies, the vast majority (83%) were prospective trials, and the most common study design was single-arm trial. Of the 43 comparative studies, 26 were randomised trials. Only three of these randomised trials (n=243) directly compared IV RhIG and IVIG,[15–17] and the latter two were available only in abstract form at the time of this review. Although these two studies have subsequently been published, the most important data were included in the abstracts, so data

Table 2: Percentage of Patients with Platelet Response

Outcome	Patients	IV RhIG			IVIG		
		t	n	MA% (95% CI)	t	n	MA% (95% CI)
Overall platelet response	All	34	761/995	79 (73–84)¶	80	1,587/1,918	86 (83–89)¶
	Acute	12	234/300	78 (70–87)¶	36	818/946	88 (85–92)¶
	Chronic	16	356/496	74 (67–81)*	23	289/349	87 (81–92)¶
Overall response at 24 hours	All	10	109/222	50 (36–65)¶	15	261/494	51 (37–64)¶
	Acute	8	93/179	53 (37–69)¶	12	246/443	55 (41–70)¶
	Chronic	2	16/43	40 (0–80)¶	1	9/14	64 (39–89)
Platelet response at 24 hours	All	5	76/138	59 (39–79)¶	9	230/358	65 (56–74)¶
with PC§ >20–30x10^9/l	Acute	5	76/138	59 (39–79)¶	9	230/358	65 (56–74)¶
	Chronic	NR	NR	NR	NR	NR	NR
Overall response within seven days	All	14	442/579	78 (71–85)¶	40	825/974	88 (84–91)¶
	Acute	5	148/182	83 (75–91)*	22	536/624	89 (85–94)¶
	Chronic	9	241/337	71 (61–81)*	10	129/158	85 (76–93)*
Platelet response at seven days	All	8	291/448	77 (66–88)¶	20	470/553	86 (82–90)*
with PC >40–50x10^9/l	Acute	3	80/93	86 (79–93)	9	294/342	87 (83–91)
(or doubling of baseline PC)	Chronic	4	71/94	77 (60–94)¶	6	71/84	85 (77–93)

*t = number of treatment groups; n = number of patients with characteristic/all patients evaluated; MA = meta-analysis; PC = platelet counts; *(p<0.10) and ¶(p<0.01) indicate significant heterogeneity; NR = not reported; IV = intravenous; RhIG = rhesus immune globulin; IVIG = intravenous immunoglobulin; CI = confidence interval.*

capture did not need to be replicated. Due to the small number of randomised studies that directly compared IV RhIG and IVIG, a pooled meta-analysis of IV RhIG and IVIG groups across all trials was conducted, regardless of study type.

Patients

Patient characteristics at baseline for each treatment type are summarised in *Table 1*. The effect of IV RhIG treatment was evaluated in 1,027 patients, and IVIG treatment in 2,063 patients. Almost 70% of all ITP patients in these studies were children (age <16 years). The IV RhIG and IVIG groups differed with regard to proportions of acute and chronic ITP patients. Chronic ITP predominated in the IV RhIG group (62%), whereas in the IVIG group the majority of patients were treated for acute ITP (64%). The vast majority of patients had primary ITP (89%). However, the prevalence of ITP secondary to HIV was approximately four times higher in the IV RhIG group than in the IVIG group (17 versus 4%). In studies reporting history of prior treatment, about 72% of IVIG-treated patients and 61% of patients in IV RhIG groups were treatment-naïve. In previously treated patients, steroids were the most common prior treatment. Approximately 17% of IV RhIG patients had previously received IVIG.

Treatment

Dosing regimens were highly variable. Of the 1,031 IV RhIG-treated patients, 9% were treated with high-dose IV RhIG (>50µg/kg), 11% received low-dose IV RhIG (<50µg/kg) and conventional doses were administered to 23% of patients. The remainder of patients (57%) received a combination of different IV RhIG doses, or dosing information was not available. Slightly more than half of patients in the IVIG groups were treated with high-dose IVIG (53%), while only 10% of patients received low-dose. Standard doses of IVIG were administered to only 3% of patients, and 33% were given a combination of different doses or dosing information was not reported.

Treatment Response

All Immune Thrombocytopenic Purpura Patients

The data were analysed with attention to overall platelet response, time to response and duration of response. The overall response to IV RhIG treatment in all ITP patients was 79%, while it was 86% in IVIG patients (see *Table 2*). Interval responses were reported in a minority of studies, and the intervals varied. About 50% of patients in each treatment group with this information responded within 24 hours. Sixty-five per cent of IVIG patients and 59% of IV RhIG patients had increased PC of >20–30x10^9/l within 24 hours. Conversely, 33% of IVIG patients and 40% of IV RhIG patients achieved platelet count recovery of greater than 40–50x10^9/l within 24 hours. An overall response within seven days was achieved by 78% of IV RhIG patients and by 88% of IVIG patients. PC increased to at least 40x10^9/l within seven days in 77% of IV RhIG-treated patients, and in 86% of IVIG-treated patients. In addition, significant heterogeneity was detected in these meta-analyses, indicating high variability in response rates among individual studies (p<0.01, test of heterogeneity). Pooled times to response, duration of response and magnitude of platelet response are presented in *Table 3*. The overall median time to response was 3.5 days (mean four days)

Table 3: Time to, Duration of and Magnitude of Platelet Response

Outcome	Patients	IV RhIG			IVIG		
		t	n	Mean (range)	t	n	Mean (range)
Overall median time to platelet response (days)	All	7	240	3.5 (1–11)	10	244	2.4 (1–6)
	Acute	3	57	2.5 (1–11)	7	178	2.3 (1–6)
	Chronic	2	109	3.4 (3–7)	2	24	2.7 (2.5–3)
Median time to PC >20–30 x10^9/l (days)	All	3	112	3.0 (1–4)	6	175	1.9 (1–3)
	Acute	2	52	1.7 (1–2)	5	133	1.5 (1–2)
	Chronic	1	11	7 (NR)	2	24	2.7 (2.5–3)
Mean duration of response (weeks)	All	8	106	6.6 (1.5–12.5)	12	207	4.7 (1.4–13.8)
	Acute	NR	NR	NR	NR	NR	NR
	Chronic	5	61	7.6 (4–12.5)	8	110	5.1 (1.4–8.8)
Median duration of response (weeks)	All	12	294	3.3 (1.3–6.6)	15	254	3.9 (1.3–12.3)
	Acute	5	107	2.9 (1.3–6.6)	6	100	5.4 (1.3–12.3)
	Chronic	4	144	3.5 (3–5.0)	7	98	2.7 (2.0–3.6)
Maximum PC (x10^9/l) (144–410)	All	11	182	148 (52–288)	31	446	183 (77–410)
	Acute	2	66	231 (177–288)	11	168	207
	Chronic	6	72	105 (70–165)	12	161	189 (89–295)

t = number of treatment groups; n = number of patients evaluated; range = range of means or medians; PC = platelet counts; NR = not reported; IV = intravenous; RhIG = rhesus immune globulin; IVIG = intravenous immunoglobulin.

following IV RhIG; however, when data were examined for WinRho-specific or IVIG treatment, the overall median and mean time to response was three days. On average, it took about three days (median) for patients in the IV RhIG group to increase platelets above 20–30x10^9/l, and two days for patients in the IVIG treatment group. The average duration of response was seven weeks (median: three weeks) after IV RhIG treatment and five weeks (median: four weeks) after IVIG treatment. These time-to-event comparisons are difficult to interpret due to the combinations of acute and chronic ITP patients. Thus, the following subgroup analyses of acute and chronic patients provide a better representation.

Acute Immune Thrombocytopenic Purpura Patients

In analysing the data for acute ITP patients, particular attention was given to the response within 24 hours, time to response and overall platelet response. When these findings are analysed separately for acute and chronic ITP, overall response was 88% in acute patients treated with IVIG and 78% in IV RhIG-treated acute patients (see *Table 2*). Fifty-three per cent of acute patients in the IV RhIG group and 55% in the IVIG group responded within 24 hours. The response within seven days was 83% for IV RhIG and 89% for IVIG patients. Time to response appeared similar in the acute patients compared with the overall ITP population, as this variable was almost exclusively reported for acute patients and not for chronic patients (see *Table 4*).

Chronic Immune Thrombocytopenic Purpura Patients

In analysing the data for chronic ITP patients, consideration was given to the overall platelet response, response at day seven and the duration of response. In chronic ITP patients, the overall response after IV RhIG treatment was 74%, and 87% for those treated with IVIG (see *Table 2*). Response data at 24 hours were sparse, but response within seven days of IV RhIG treatment was 71%, and in the IVIG group, 85%. PC increased to at least 40–50x10^9/l or two-fold over baseline within seven days in 77% of IV RhIG patients overall, in 86% in WinRho-specific studies, and in 85% of IVIG patients. As discussed above, time to platelet recovery was not reported in the vast majority of studies in chronic ITP patients; however, duration of response was an important element reported in these patients (see *Table 3*). The mean duration of response following IV RhIG was 7.6 weeks (median: 3.5 weeks), and 5.1 weeks (median: 2.7 weeks) following IVIG.

> Further direct comparison in trials in similar patient populations, especially children with chronic immune thrombocytopenic purpura, would be valuable.

Randomised Intravenous Rhesus Immune Globulin versus Intravenous Immunoglobulin Trials

Three randomised trials directly comparing IV RhIG with IVIG were identified.[15–17] Two of the trials[15,17] evaluated WinRho and IVIG treatments in acute ITP in children. The Tarantino study (in abstract form) compared two doses of WinRho (50cg/kg and 75mcg/kg) versus low-dose IVIG (0.8g/kg) in newly diagnosed ITP in children. The response rate (PC>20x10^9/l) at 24 hours was 50 and 72% for the groups treated with standard and high-dose WinRho, respectively, and for the IVIG group it was 77%. At 72 hours, the response for both high-dose WinRho and IVIG was 81 and 78%, respectively, in the 50mcg/kg WinRho dose group. Fewer side effects were observed with WinRho standard dose compared with high-dose WinRho and IVIG in this study. Authors in the Blanchette study compared two doses of IVIG (1g/kg x 2 and 0.8g/kg) versus WinRho (25mcg/kg x 2) versus prednisolone in an acute ITP paediatric population. At 72 hours, 94% of children in the IVIG (1g/kg) group, 97% in the 0.8g/kg IVIG group and 82% of WinRho-treated patients increased PC to >20x10^9/l. The percentage of children increasing PC≥50x10^9/l was 88, 83 and 68% for the two IVIG and WinRho groups, respectively. The mean time to PC >20x10^9/l was 2.9 days for IVIG (1g/kgx2), 1.4 days for IVIG (0.8g/kg) and 3.9 days for WinRho. For PC ≥50x10^9/l, the mean time was 2.8, 3.4 and 6.9 days, respectively. The side effects were comparable in the IVIG and WinRho groups, except that a greater proportion of children in the WinRho group had haemoglobin decrease to <100g/l (24 versus 12 and 6%, respectively). A chronic ITP paediatric population was evaluated in the El Alfy study comparing WinRho (50mcg/kg) versus low-dose IVIG (250mg/kg), and only limited data were available at the time of the analysis. Response to treatment (PC ≥50x10^9/l or doubling of baseline PC) was observed in 33 and 37.5% of WinRho and IVIG patients, respectively, on day three; on day seven, the response rate was 67% and 75%, respectively. The mean haemoglobin decrease of 0.8g/dl was observed in patients treated with WinRho.

Safety Outcomes

Results of the safety analyses are displayed in *Table 4*. No deaths have been reported in the IV RhIG studies. Treatment discontinuations due to adverse events (AEs) were rarely reported, but in the groups that did report this information the rate was 3–4%. Studies presented AE most frequently as percentage of patients having AE, a specific listing of AE or a percentage of patients having fever, nausea, headaches and vomiting. The most commonly observed AEs during treatment with IV RhIG and IVIG were chills (19 and 11%, respectively), fever (10% for IV RhIG and 13% for IVIG) and headache (14 and 26% for IV RhIG and IVIG, respectively), while a combination of fever, nausea, vomiting or headache was reported in about 5% of IV RhIG and 21% of IVIG patients. One of the most common side effects of IV RhIG treatment is haemolysis, which was often reported as a mean decrease in haemoglobin. A mean haemoglobin decrease of 1g/dl was observed in the IV RhIG group, while a decrease of 0.5g/dl was reported in IVIG patients in the few studies assessing this end-point. Although no deaths were reported in any of the 30 IV RhIG studies included in this review, in a publication by Gaines[18] five deaths were reported to be caused by WinRho administration in ITP patients. Three deaths were reported in the 69 evaluated IVIG studies.

Discussion

The goal of this systematic review was to evaluate the efficacy and safety of IV RhIG and IVIG in the treatment of ITP using published evidence, including meeting abstracts. To our knowledge, this is the first systematic review of the subject that compares these first-line treatment modalities. It spanned from 1985 to 2005 and included 89 studies that provided response and/or safety information in 3,127 patients. There are only three direct randomised comparison trials of IV RhIG and IVIG available.[15–17] Blanchette et al.[15] reported that IVIG was superior to IV RhIG in children who are severely thrombocytopenic and who may be actively bleeding. The subsequent assessment of the study by Zunich et al.[19] found flaws in the data analysis by Blanchette et al.[15] Of primary concern, the dose of IV

The European School of Haematology is a non-profit interdisciplinary institution for continuing education.

UPCOMING CONFERENCES 2008

29 February-2 March, 2008 - Paris, France
ESH-EHA Hematology Tutorial
FOCUS ON ANEMIA AND MYELODYSPLASIA
Chairs: **B. Bain, R. Foà, G. Zini**

6-9 March, 2008 - Cascais, Portugal
ESH International Conference
MULTIPLE MYELOMA and OTHER MONOCLONAL GAMMOPATHIES
Chairs: **J.L. Harousseau, J. San Miguel, M. Boccadoro**
Local Organizer: **A. Parreira**

11-13 April, 2008 - Mandelieu, France
ESH-EHA Scientific Workshop
BIOMARKERS AND PROGNOSIS IN MALIGNANT LYMPHOMAS
Chairs: **A. Hagenbeek, R. Gascoyne, G. Salles**
EHA scholarships are available

30 April-4 May, 2008 - Croatia
ESH-EBMT Training Course
HAEMOPOIETIC STEM CELL TRANSPLANTATION
Chairs: **J. Apperley, E. Gluckman, E. Carreras, A. Gratwohl, T. Masszi**
Local Organizer: **B. Labar**

9-12 May, 2008 - Paris, France
ESH Euroconference
ANGIOGENESIS
Chairs: **K. Alitalo, A. Bikfalvi, Ch. Betsholtz, A. Eichmann, C. Rüegg, G. Tobelem**

15-18 May, 2008 - Albufeira, Portugal
ESH International Conference
MYELODYSPLASTIC SYNDROMES and BONE MARROW FAILURE
Chairs: **P. Fenaux, E. Gluckman, E. Hellström-Lindberg, M. Cazzola**
Local Organizer: **A. Almeida**

30 June-2 July, 2008 - Mandelieu, France
ESH-EHA Scientific Workshop
MESENCHYMAL STEM CELLS
Chairs: **W.E. Fibbe, K. Le Blanc, F. Frassoni, C. Verfaillie**

5-7 September, 2008 - Boston, USA
ESH International Conference on
CHRONIC MYELOID LEUKEMIA
Organizers: **J.M. Goldman, J. Cortes**
Co-Organizers: **A.M. Carella, G. Daley, F. Guilhot, R. Hehlmann, M. Horowitz, J.V. Melo, G. Saglio, C. Schiffer, P. Valent**

18-20 September, 2008 - Athens, Greece
ESH Euroconference
MYELOPROLIFERATIVE DISORDERS
Chairs: **T. Barbui, A.R. Green, H.L. Pahl, R. Skoda, W. Vainchenker**

3-5 October, 2008 - Mandelieu, France
ESH-EHA Scientific Workshop
BIOLOGY OF ACUTE MYELOID LEUKEMIA
Chairs: **H. Döhner, B. Löwenberg**
EHA scholarships are available

17-19 October, 2008 - Mandelieu, France
ESH-Eucord-Netcord-EBMT UT MD Anderson Cancer Center
BIOLOGY AND CLINICAL APPLICATIONS OF CORD BLOOD CELLS
Chairs: **E. Gluckman, J. Kurtzberg, E.J. Shpall, J. Garcia**

30 October-4 November, 2008 - Cascais, Portugal
ESH Euroconference
CELL DEATH AND DISEASE
ADVANCES IN THERAPEUTIC INTERVENTION AND DRUG DEVELOPMENT
Chairs: **T.J. McDonnell, J.A. Hickman, K.M. Debatin**

6-9 November 2008 - Albufeira, Portugal
ESH International Conference
CHRONIC LYMPHOCYTIC LEUKAEMIA
Chair: **E. Montserrat**

14-15 November, 2008 - Dublin, Ireland
ESH-EHA HEMATOLOGY TUTORIAL ON
MYELOID MALIGNANCIES
Chair: **S. McCann**

Scholarships are available for most ESH conferences

For full information go to: www.esh.org

FREE EDUCATIONAL TOOLS

ESH-CGRF HANDBOOK on
Disorders of Iron Homeostasis, Erythrocytes and Erythropoiesis
Editors: **C. Beaumont, Ph. Beris, Y. Beuzard, C. Brugnara**
If you would like a copy, please contact: celine.caudroit@univ-paris-diderot.fr

NEW!

The curriculum in Iron Metabolism and Related Disorders.
Now available on the ESH website : **www.esh.org**

NEW!

In 2008
Revised edition ESH-EBMT Handbook on Haemopoietic Stem Cell Transplantation
Editors: **J. Apperley, E. Carerras, E. Gluckman, A. Gratwohl, T. Masszi**

NEW!

In 2009
ESH Handbook on Chronic Myeloid Leukaemia
Senior Editor: J.M. Goldman

EUROPEAN SCHOOL OF HAEMATOLOGY
Centre Hayem, Hôpital Saint-Louis - 1, av. Claude Vellefaux, 75475 Paris Cedex 10, France
Tel. (33) 1 42 06 65 40 - Fax (33) 1 42 06 05 87
e.mail: ghyslaine.lebougault@univ-paris-diderot.fr **OR** marie-france.simon@univ-paris-diderot.fr
OR celine.caudroit@univ-paris-diderot.fr
visit our website : www.esh.org

Table 4: Incidence of Adverse Events

Outcome	IV RhIG			IVIG		
	t	n	MA% (95% CI)	t	n	MA% (95% CI)
Total patients evaluated	36	1,030	–	85	2,092	–
Treatment discontinuations due to adverse events	2	1/28	4 (0–11)	15	15/288	3 (0–7)
Number of patients with:						
Headache	7	28/137	14 (2–26)*	23	151/594	27 (17–36)
Fever	9	23/137	10 (2–18)*	21	75/524	13 (7–18)*
Chills	5	25/122	19 (8–31)*	4	16/172	11 (0–24)*
Vomiting	7	0/28	0 (0–7)	7	28/266	11 (1.4–20)*
Composite	6	7/118	5 (0–10)*	12	56/259	21 (10–32)*
Aseptic meningitis	3	0/86	0 (0–2)	8	9/256	3 (1–5)
Bleeding	7	2/152	1 (0–4)	13	73/296	14 (0.4–28)*
Dyspnoea	NR	NR	NR	3	4/61	7 (0.4–13)
Asthaenia	2	0/28	0 (0–7)	3	5/114	4 (0.5–8)
Post-treatment haemoglobin change (mg/dl)	12	462	-1 (-1.4 to -0.7)*	3	66	-0.5 (-0.9 to -0.1)§

*t = number of treatment groups; n = number of patients with characteristic/all patients evaluated; MA = meta-analysis; §(p<0.10) and *(p<0.01) indicate significant heterogeneity; composite includes any combination of fever, nausea, vomiting or headache; NR = not reported; CI = confidence interval; IV = intravenous; RhIG = rhesus immune globulin; IVIG = intravenous immunoglobulin.*

RhIG used in this study on day one was only 25mcg/kg, biasing the study against immediate efficacy following IV RhIG. El Alfy et al.[16] concluded that single doses of both IV RhIG and low-dose IVIG effectively increased PC in children with chronic ITP at risk of bleeding. In addition, repeated doses of IV RhIG could maintain PC above critical values or double baseline counts in nearly two out of three of the patients showing good control of bleeding. They, in contrast, used a low dose of IVIG, but this dose was validated in children with acute ITP in a separate study.[20] Tarantino et al.[17] concluded that a single 75µg/kg dose of IV RhIG raised the platelet count in children with newly diagnosed ITP more rapidly than standard-dose IV RhIG and as effectively as IVIG, with an acceptable safety profile. Therefore, the three studies with direct data comparisons in general support approximately equivalent efficacy of IV RhIG and IVIG, while pointing out the dose dependency of the IV RhIG response.

The limitations of the overall review include the variety of dosing regimens and the wide variation in the response definitions among studies. The definition of response ranged from a small increase in platelets from baseline to increases as high as 150x10^9/l, and significant heterogeneity was detected among the studies analysed. Factors such as study design, differences in ITP patient populations and disease severity at baseline (acute and chronic, adults or children, treatment-naïve or treatment-refractory, etc.), various treatment doses and treatment duration all may have influenced the response rates. Some notable differences between the IV RhIG and IVIG groups were observed that may have potential influence on the study results. The majority of IVIG patients had acute ITP and were treated with high IVIG doses, while the majority of IV RhIG patients suffered from chronic ITP and were predominantly treated with conventional or low doses of IV RhIG. In acute ITP patients it is important to increase the PC as quickly as possible, and in chronic ITP patients it is important to maintain the PC above a certain number, i.e. 20 or 30x10^9/l. The proportion of acute to chronic patients may in part confound the results between study groups as the higher percentage of acute ITP patients in the IVIG group may yield a better overall response. In addition, a greater proportion of IV RhIG patients had HIV-related ITP and have received prior ITP treatment – factors that could potentially lead to lower response rates as well. Furthermore, meta-analyses of continuous response outcomes (time to response and duration of response) were planned but not performed due to the high variability of response definition and lack of reporting of mean values and variances. Median values for continuous variables were often presented in these studies, which on the one hand provide a better understanding of the population means, but on the other hand are not useful for statistical testing in a meta-analytical context. Finally, at the time this study was undertaken, the vast majority of studies were low-quality, non-randomised, single-arm studies or retrospective chart reviews.

Conclusion

We addressed the evidence gap regarding the efficacy and safety of IV RhIG and IVIG in ITP patients. This systematic review summarises the available evidence published between 1985 and 2005. In the aggregate, data are based on 89 studies evaluating more than 3,100 patients. In acute ITP, where it is important to increase PC as quickly as possible, 53% of the patients in the IV RhIG group and 55% of those in the IVIG group responded within 24 hours of treatment. Similarly, in chronic ITP – where it is important to keep the PC high for as long as possible – the mean duration of response was eight weeks after IV RhIG and five weeks following IVIG treatment. Although limited safety information was available in these studies, both IV RhIG and IVIG appear to have similar safety profiles. Further direct comparison in trials in similar patient populations, especially children with chronic ITP, would be valuable in further refining the comparative efficacy and safety of IV RhIG versus IVIG in these patients. ■

Acknowledgement

This work was sponsored by Cangene Corporation.

1. McMillan R, *N Engl J Med*, 1981;304:1135.
2. Kelton JG, Gibbons S, *Semin Thromb Haemost*, 1982;8:83.
3. George JN, Woolf SH, Raskob GE, et al., *Blood*,1996;88:3–40.
4. Lilleyman JS, *Arch Dis Chil*, 1994;94:909–13.
5. Cines DB, Blanchette VS, *N Engl J Med*, 2002;346:995–1008.
6. Simpson KN, Coughlin CM, et al., *Semin Hematol*, 1998;35:58–64.
7. Scaradavou A, Woo B, et al., *Blood*, 1997;89:2689–2700.
8. Chalmers TC, Lau J, *Stat Methods Med Res*, 1993;2:161–72.
9. Cook DJ, et al., *Ann Intern Med*, 1997;126:376–80.
10. Alderson P, Green S, Higgins JPT, (eds), Cochrane Collaboration Handbook 4.2.1 [updated December 2003]. In: *The Cochrane Library*, Issue 1, Chichester: John Wiley & Sons, Ltd, 2004.
11. DerSimonian R, Laird N, *Control Clin Trials*, 1986;7:177–88.
12. Barrios NJ, Humbert JR, McNeil J, *Acta Haematol*, 1993;89:6–9.
13. Nomura S, et al., *Int J Hematol*, 1996;63:227–34.
14. George JN, et al., *Am J Hematol*, 2003;74:161–9.
15. Blanchette V, Imbach P, et al., *Lancet*, 1994;344:703–7.
16. El Alfy MS, et al., *Acta Haematol*, 2006;115:46–52.
17. Tarantino MD, Young G, et al., *J Pediatr*, 2006;148:489–94.
18. Gaines AR, *Blood*, 2005;106(5):1532–7.
19. Zunich KM, Harkonen WS, et al., *Lancet*, 1995;346:1363–4.
20. Warrier I, et al., *J Pediatr Hematol Oncol*, 1997;19(3):197–201.