Hematopoietic growth factors in aplastic anemia patients treated with immunosuppressive therapy-systematic review and meta-analysis

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ABSTRACT

Immunosuppressive therapy is the treatment for aplastic anemia patients ineligible for transplantation. The role of hematopoietic growth factors as adjunct to treatment in these patients is unclear. We conducted a systematic review and meta-analysis of randomized controlled trials comparing treatment with immunosuppressive therapy and hematopoietic growth factors to immunosuppressive therapy alone in patients with aplastic anemia. Two reviewers appraised the quality of trials and extracted data. For each trial, results were expressed as relative risks with 95% confidence intervals (CI) for dichotomous data. The addition of hematopoietic growth factors yielded no difference in overall mortality at 100 days, one year and five years [relative risks 1.33 (95% CI 0.56-3.18), relative risks 0.90 (95% CI 0.50-1.63) and relative risks 0.89 (95% CI 0.55-1.46), respectively]. There was no difference in overall hematologic response and in the occurrence of infections. HGF significantly decreased the risk for relapse, relative risks 0.45 (95% CI 0.30-0.68, 3 trials). Hematopoietic growth factors were not associated with higher occurrence of myelodysplastic syndrome and acute myeloid leukemia or paroxysmal nocturnal hemoglobinuria. The addition of hematopoietic growth factors does not affect mortality, response rate or infections occurrence. Therefore, it should not be recommended routinely as an adjunct to the immunosuppressive therapy for patients with aplastic anemia.

Key words: hematopoietic growth factors, aplastic anemia, immunosuppressive therapy.

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Introduction

Aplastic anemia is a rare disorder characterized by pancytopenia and hypoplastic bone marrow.[1] Entities of aplastic anemia which require specific treatment include severe aplastic anemia and very severe aplastic anemia,[2,3] although some authorities recommend treatment for non-severe aplastic anemia as well.[3-5] The preferred treatment for severe and very severe aplastic anemia is allogeneic hematopoietic stem cell transplantation (allo-HSCT).[6-8] However, this treatment is not always applicable, due to unavailability of matched HLA donors and age restriction of the recipients. The alternative to allo-HSCT is immunosuppressive therapy (IST) consisting of antithymocyte globulin (ATG)/antilymphocyte globulin (ALG) and/or cyclosporine A (CsA) with or without the addition of hematopoietic growth factors (HGF).

HGF include both hematopoietic colony stimulating factors, i.e. granulocyte colony stimulating factor (G-CSF) and granulocyte-monocyte colony stimulating factor (GM-CSF), and erythropoiesis stimulating agents, i.e. erythropoietin (EPO). The rationale for using hematopoietic colony stimulating factors in aplastic anemia is based on their ability to stimulate production of neutrophil precursors, to enhance function of the mature neutrophils and to ameliorate neutropenia and its complications. Furthermore, their use may also improve response to IST, as they may act in concert with endogenous HGF to stimulate hematopoietic stem cells.[5,9-12] The addition of erythropoiesis stimulating agents to hematopoietic colony stimulating factors is aimed at encouraging hemoglobin production and synergizing the stimulation of other lineage precursors.[13]

Several prospective randomized controlled trials evaluated the role of HGF in aplastic anemia. These studies were incon-

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clusive regarding their effect on hematologic response and the incidence of infections. Most of them could not show a survival benefit.[4,14-17] Furthermore, secondary clonal disorders, mainly clonal evolution to myelodysplastic syndrome (MDS) or to acute myelogenous leukemia (AML) were of concern in some of the trials.[11,18,19]

We undertook this systematic review and meta-analysis in order to assess the role of the addition of HGF to IST in aplastic anemia, mainly severe aplastic anemia, and specifically to evaluate their effect on mortality, overall hematologic response and on the occurrence of MDS/AML and paroxysmal nocturnal hemoglobinuria (PNH).

Design and Methods

Data sources and searches

We searched PubMed (January 1966 to March 2008), The Cochrane Library (issue 2/2008), LILACS and the following conference proceedings for recently conducted trials in hematology: Annual Meeting of the American Society of Hematology (2002-2007), European group for Bone and Marrow Transplantation (2002-2008), Annual Meeting of the European Hematology Association (2002-2007) and the Annual Meeting of the Society for Hematology and Stem Cells (2002-2007). In addition, we searched databases of ongoing and unpublished trials: *http://www.controlled-trials.com, http://www.clinicaltrials.gov/ct*, *http://clinicaltrials.nci.nih.gov*.

We used the following search terms: erythropoietin [MeSH] or erythropoietin or erythropoiesis stimulating factor or erythropoiesis stimulating factor [MeSH] or hematopoietic growth factor [MeSH] or hematopoietic growth factor or colony stimulating factor or colony stimulating factor [MeSH] or granulocyte colony stimulating factor [MeSH] or granulocyte colony stimulating factor and aplastic anemia[MeSH] or aplastic anemia. For PubMed, we added The Cochrane highly sensitive search term for identification of clinical trials.[20] We scanned the references of all included studies and reviews identified for additional trials that did not come up in our search.

Study selection

We included all randomized, controlled trials in patients with acquired aplastic anemia treated with IST, which compared between the addition of HGF and placebo or no treatment (control).

HGF included any of the following: G-CSF alone, GM-CSF alone, G-CSF or GM-CSF with EPO.

We included trials regardless of publication status, date of publication and language. One author (RG) screened all references identified through our search strategy; two reviewers (RG, AG) independently inspected each abstract and applied inclusion criteria. For possibly relevant articles or in the event of disagreement between the two reviewers, we obtained and independently inspected the full article.

Data extraction and quality assessment

Two reviewers independently extracted data from included trials. In the event of disagreement between the two reviewers (RG, AG), a third reviewer (PR) extracted the data and a decision was reached by consensus. We contacted the authors of trials for missing data when necessary. We assessed allocation concealment, allocation generation and blinding and graded allocation concealment and generation as adequate, unclear, inadequate or not used according to the criteria specified in the Cochrane Handbook.[20]

Definition of outcomes

The primary outcome was overall mortality at 100 days, one year, five years or end of follow-up. Secondary outcomes included hematologic response (overall, complete, partial) or no response (i.e. refractory) at three and 12 months, clinically documented infections, severe infections, relapse, adverse events and secondary clonal disorders including: clonal evolution (defined as the occurrence of MDS or AML) and PNH, at the end of follow-up.

Data synthesis and analysis

For each trial, results were expressed as relative risks (RR) with 95% confidence intervals (CI) for dichotomous data (*Review Manager (RevMan), version 4.2 for Windows; the Cochrane Collaboration, Oxford, United Kingdom*). Outcomes were extracted preferentially by intention-to-treat, including all individuals randomized in the outcome assessment. Where impossible, data by available

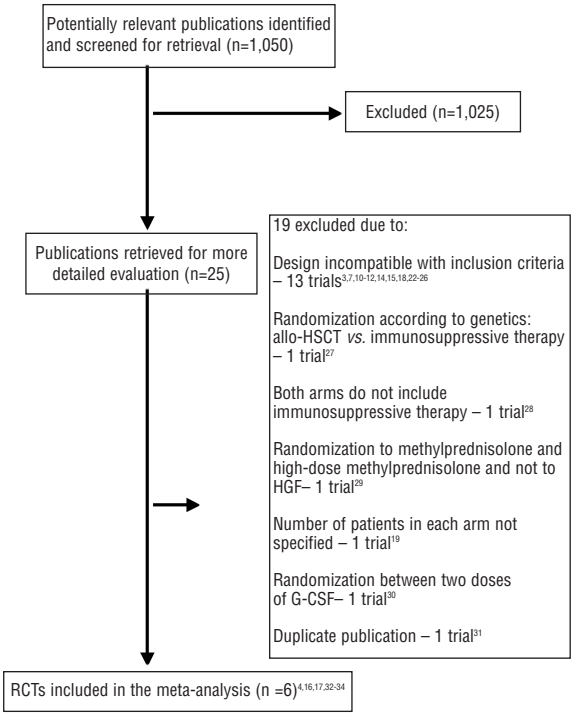

Figure 1. Flow diagram: publications identified for study and exclusions.

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case analysis were extracted. For the main analysis, all trials were pooled.

We assessed for heterogeneity in the results of the trials using a χ^2 test of heterogeneity (p<0.1) and the I^2 measure of inconsistency. We conducted meta-analysis using a fixed-effect model, except when statistically significant heterogeneity was found (p<0.10 or I^2>50%), in which case we chose a random-effects model and used the DerSimonian and Laird method (RRs>1 favor control).[21]

We performed sensitivity analyses to assess the effect of individual methodological quality measures on effect estimates, including allocation generation, concealment and blinding.

Results

The computerized search strategy identified 1050 trials, 25 of which were considered relevant for this review. Of them, 19 trials were excluded for various reasons[3,7,10-12,14,15,18,19,22-31] (Figure 1). Six trials performed between 1991-2007 and randomizing 414 patients fulfilled inclusion criteria.[4,16,17,32-34] Another relevant abstract from a recent conference proceeding was not included since results are still pending.[35] Table 1 describes the inclusion criteria of the included trials and definitions of response criteria for each trial. Table 2 describes characteristics of included trials. Although our search strategy included the full spectrum of acquired aplastic anemia, only one study reported on patients with non-severe aplastic anemia.[4] This study included 64 patients; of them, 28 patients had non-severe aplastic anemia and 36 patients had severe aplastic anemia.

IST regimens consisted of the combination of ATG or ALG with CsA and steroids in four trials.[4,16,17,32] ATG or ALG and steroids in two trials[33,34] and CsA alone in one trial[34] (Table 2). The hematopoietic growth factor used in three trials was G-SCF,[4,16,32] in one trial GM-CSF[33] and in two trials GM-CSF and erythropoietin.[17,34] The etiology of aplastic anemia in most patients was idiopathic. As for the methodology of the trials, only one of the six studies was double blinded.[33] All but two trials[4,32] reported outcomes by intention to treat analysis.

Primary outcome

All six trials reported overall mortality, five of them at 100 days,[4,16,17,32,34] five trials at one year,[4,17,32-34] and three trials at five years.[16,17,32] There was no difference in overall mortality between patients treated with IST and HGF and those treated with IST and control. At 100 days, RR 1.33 (95% CI 0.56-3.18, 5 trials) [no significant heterogeneity (p=0.58, I^2=0%)], at one year, RR 0.90 (95% CI

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Table 1. Inclusion criteria and definitions of response criteria and time for assessment of included trials.

Study, (ref)	Inclusion Criteria	Definition of complete response	Definition of partial response	Time for mortality assessment	Time for hematologic response assessment
Teramura, 2007[32]	Acquired SAA as defined by international criteria[2]:* Age 18-75, Newly diagnosed No specific prior therapy	Neut.>1.5×10⁹/L, Plt>150×10⁹/L, Hb>11 g/dL	Transfusion independence Disease no longer severe	3 m, 6 m, 12 m, 4 y	3 m, 6 m, 12 m, 4 y
Zheng, 2006[17]	SAA as defined by International criteria[2]*	Transfusion independence, Neut. >1.5×10⁹/L, Plt. >100×10⁹/L, Hb>11 g/dL	Transfusion independence Neut.>0.5×10⁹/L; Plt.>20×10⁹/L; Hb>8 g/dL	3 m, 12 m, 5 y	3 m, 6 m
Gluckman, 2002[16]	*De novo* idiopathic SAA Age >1 year Diagnosis made 1 month before entry SAA as defined by International criteria[2]*	Neut.>1.5×10⁹/L	1.5×10⁹/L >Neut.>0.5×10⁹/L	3 m, 6 m, 5 y	3 m, 5 y
Kojima, 2000[4]	Age< 18, Recently diagnosed within 180 days without prior treatment NSAA: Neut <1×10⁹/L; Plt <50×10⁹/L; Ret <60×10⁹/L; SAA as defined by International criteria[2]*	Neut.>1.5×10⁹/L, Plt>100×10⁹/L, Hb>11 g/dL	PR in severe AA patients: Neut.>0.5×10⁹/L; Plt.>20×10⁹/L; Hb>8 g/dL PR in moderate AA patients: Neut.>1×10⁹/L; Plt.>30×10⁹/L; Hb>8 g/L	3 m, 6 m, 12 m	3 m, 6 m, 12 m
Shao, 1998[34]	Newly diagnosed SAA as defined by International criteria[2]*	Neut.>1.5×10⁹/L, Hb>12 g/dL, Plt>80×10⁹/L	Neut.>0.5×10⁹/L Hb>8 g/dL; Plt>20×10⁹/L	3 m, 6 m, 12 m	3 m, 6 m, 12 m
Gordon-Smith, 1991[33]	SAA as defined by International criteria[2]*	Independence of transfusions, Neut.>2×10⁹/L, Plt>100×10⁹/L	Transfusion independence	12 m	3 m

*SAA: severe aplastic anemia; NSAA: non-severe aplastic anemia; Plt: platelets; Ret: reticulocytes; Neut: neutrophils. *International criteria[2]: hypoplastic BM (cellularity< 25%) and at least 2 of the 3 following: Neut<0.5×10⁹/L; and/or Plt <20×10⁹/L; and/or corrected Ret. Count of less than 1%; SAA: severe aplastic anemia; NSAA: non-severe aplastic anemia; Plt: platelets; Ret: reticulocytes; Neut: neutrophils; Hb: hemoglobin; CR: complete response; PR: partial response; m: months; y: years.*

0.50-1.63, 5 trials) [no significant heterogeneity (p=0.18, I^2=36.8%)] and at five years, RR 0.89 (95% CI 0.55-1.46, 3 trials) (no significant heterogeneity [p=0.83, (I^2=0%)] (Figure 2). Sensitivity analysis for mortality rate at 100 days showed a higher RR (favoring control) with adequate allocation concealment and generation, RR 1.57 (95% CI 0.44-5.55, 3 trials) compared to unclear methods, RR 1.15 (95% CI 0.34-3.84, 2 trials), without a statistically significant result or difference between the subgroups.

Secondary outcomes

There was no difference in overall hematologic response between IST with or without HGF at three months, RR 1.13 (95% CI 0.88-1.45, 6 trials) and at 12 months, RR 1.21 (95% CI 0.78-1.86, 3 trials) (Figure 3). Similarly, there was no difference in complete hematologic response with or without HGF at three months, RR 1.39 (95% CI 0.77-2.52, 4 trials) and at 12 months, RR 1.54 (95% CI 0.62-3.83, 3 trials). All the comparisons of hematologic response were significantly heterogeneous with I^2 values>50%.

HGF administration compared with placebo or no intervention did not alter the occurrence of refractory disease, RR 0.71 (95% CI 0.40-1.26, 5 trials) [significant heterogeneity was found (p=0.01, I^2=68.1% random effects model)]. The risk for relapse throughout the study period, however, was significantly decreased by the use of HGF, RR 0.45 (95% CI 0.30-0.68, 3 trials) [no significant heterogeneity (p=0.92, I^2=0%)] (Figure 4). For most trials the duration of HGF was less than three months, while relapse was evaluated at 4-5 years,[4,16,32] namely when patients were off treatment.

HGF administration did not decrease the occurrence of clinically documented infections when compared to control, RR 1.10 (95% CI 0.90-1.33, 5 trials) (no significant heterogeneity was found p=0.27 I^2=24.2%). Similarly, there was no difference in the occurrence of severe infections when compared to control RR 0.88 (95% CI 0.58-1.34, 4 trials) (no significant heterogeneity was found p=0.52, I^2=0%).

HGF were not associated with statistically significant higher occurrence of MDS and AML or PNH. As shown in Figure 5, the addition of HGF to IST was not associated with a higher occurrence of clonal evolution into MDS/AML, RR 1.59 (95% CI 0.39-6.51, 5 trials) (no sig-

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Table 2. Characteristics of included trials.

Study, (ref.)	Intervention (type of IST, HGF - type, dose, schedule)	pts. n	Age (yrs.) median (range)	N. of pts. with NSAA/ SAA/ VSAA	Baseline neut. count (x10^9/L)	Allocation generation, concealment
Teramura, 2007[32]	Horse ATG + CsA + prednisolone	48	53 (19-74)	0/36/11	0.30	B, B
	Horse ATG + CsA + prednisolone + IV filgastrim 400 μg/day or lenograstim 50 μg/day, every other day till day 28 and then once or twice a week till day 84	47	54 (19-75)	0/29/19	0.32	
Zheng, 2006[17]	Horse-ATG + CsA + prednisolone	47	35 (8-71)	0/33/14	0.39	A, A
	Horse-ATG + CsA + prednisolone - s.c rhuGM-CSF 5 μg/kg/d+ s.c rhuEPO 100 U/kg/d 3 d in a week for first mo, 2 d in a week for second mo and 1 d in a week for third mo	30	36 (5-68)	0/19/11	0.43	
Gluckman, 2002[16]	ATG (horse or rabbit) + CsA + prednisolone	49	22 (1-82)	0/30/19	0.2	B, B
	ATG (horse or rabbit) + CsA + prednisolone + s.c. lenograstim 5 μg/kg/d for 98 days	53	26 (2-71)	0/27/26	0.2	
Kojima, 2000[4]	Horse ATG + CsA+ methylprednisolone	34	9 (1-15)	13/18/0	0.46	A, A
	IV horse ATG + CsA + methylprednisolone + s.c./IV G-CSF 400 μg/m^2 for 90 days	35	8 (2-16)	15/18/0	0.48	
Shao, 1998[34]	Horse ALG + prednisone	11	32 (21-67)	NA	NA	A, A
	CsA	8	26 (9-45)	NA	0.41	A, A
	Horse ALG + prednisone + s.c. GM-CSF 300 μg + IV EPO 6000 units for 3 months	11	34 (23-63)	NA	NA	
	CsA + s.c.GM-CSF 300 μg + IV EPO 6000 U for 3 months	8	28 (12-42)	NA	0.40	
Gordon-Smith, 1991[33]	IV ALG (source varied) + corticosteroids (dose varied)	14	42	NA	0.54	B, B
	IV ALG (source varied) + corticosteroids (dose varied)+ IV continuous rhGMCSF 300 mcg/S.C rhGMCSF 100 μg x 2/d for 28 days	13	32	NA	0.69	

ATG: anti-thymocyte globulin; ALG: anti-lymphocyte globulin; CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte -monocyte colony stimulating factor; EPO: erythropoietin; IST: immunosuppressive therapy; HGF: hematopoietic growth factors; AA: aplastic anemia; VSAA: very severe aplastic anemia; CBC: complete blood count; Plt.: platelets.

nificant heterogeneity was found p=0.91, I^2=0%). There were 5 cases of clonal evolution in the HGF arm including one case of AML and 4 cases of MDS while there were 3 cases of MDS in the control arm. With respect to PNH, there was no statistically significant higher occurrence of PNH with HGF (RR 3.5)95% CI 0.86-14.24, 5 trials) [no significant heterogeneity was found (p=0.58), I^2=0%]. There were 7 cases in the HGF arm and 2 cases in the control arm (Figure 5).

When we conducted a separate analysis for G-CSF and GM-CSF, there was no statistically significant difference in the rate of secondary clonal disorders between the HGF arms and control.

There was no difference in total adverse events between IST with or without HGF: RR 1.49 (95% CI 0.78-2.84, 5 trials) (significant heterogeneity was found (p=0.001, I^2=78%, random effects model). There was not enough data regarding severe adverse events, grade 3-4.

Discussion

Our systematic review demonstrates that treatment with HGF does not affect mortality rate or improve complete and overall hematologic response in patients with aplastic anemia requiring IST. Likewise, it does not alter the occurrence of refractory disease, the rate of clinically documented or severe infections but is associated with a decreased risk for relapse. An interesting finding was the higher occurrence of clonal evolution with the administration of HGF, which nearly approached a statistical significance.

These results are in accordance with the 2003 treatment guidelines for the diagnosis and management of acquired aplastic anemia[5] which do not recommend the routine use of HGFs and restrict their use to clinical trials only.

Locasciulli *et al.* reported no survival advantage for higher *vs.* lower doses of G-CSF added to IST.[30] Our results further emphasize the lack of a clinical and biological effect of HGF at any dose level in aplastic anemia.

The development of secondary clonal disorders after treatment with IST for aplastic anemia is well recognized. About 5-15% of long-term survivors with aplastic anemia, treated even before the era of growth factors administration, developed this complication. It is hypothesized that some of the patients diagnosed as suffering from aplastic anemia actually had a clonal disorder such as hypoplastic MDS or PNH *a priori* and the occurrence of a secondary clonal disorder was in fact part of the natural course of their disease.[36-39]

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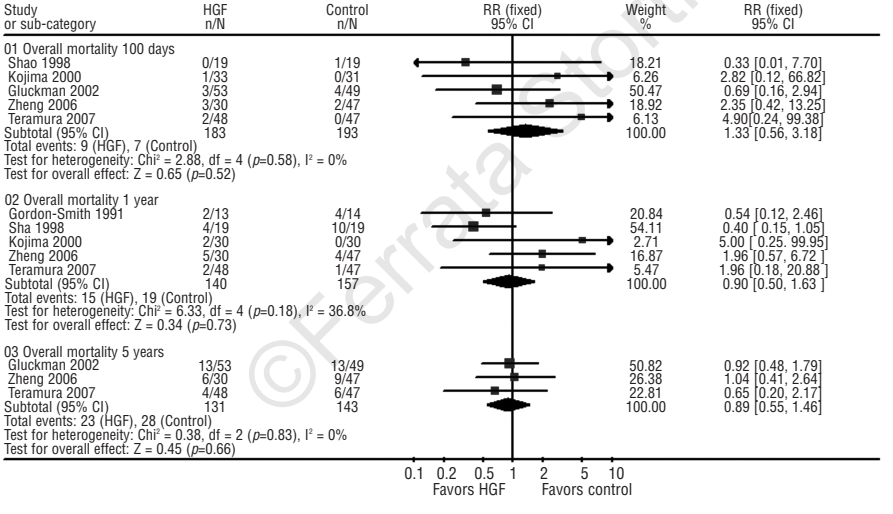

Figure 2. Overall mortality comparing between patients treated with IST and HGF and those treated with IST and control at 100 days, one year and five years.

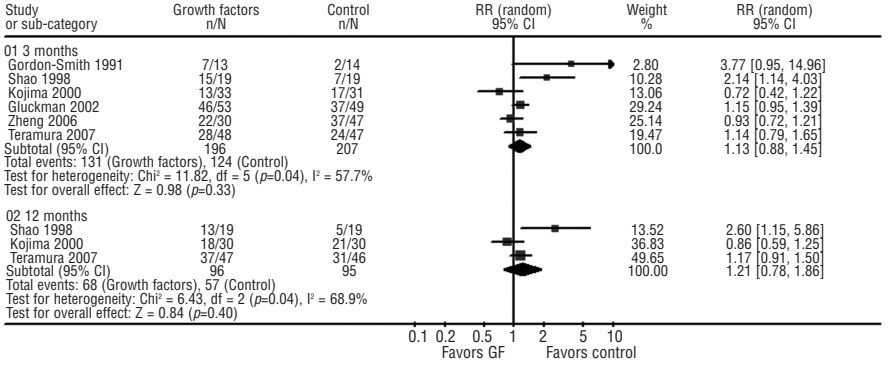

Figure 3. Overall hematologic response comparing between patients treated with IST and HGF and those treated with IST and control.

A higher risk of clonal evolution either into a genetic abnormality or into a transformation to MDS/AML with growth factors has been reported by a retrospective European study[25] and by several reports from Japan.[40,41] Ohara *et al*.[41] and Rosenberg *et al*.[42] showed a correlation between the cumulative dose of HGF and the development of clonal evolution to MDS/AML in patients with aplastic anemia and severe congenital neutropenia, supporting a deleterious effect of growth factors on the development of clonal evolution.

A biological mechanism, which could explain the evolution of a clonal hematologic neoplasm in aplastic anemia augmented by the use of growth factors, is genetic instability, manifested by the frequent occurrence of cytogenetic abnormalities during the course of the disease.[43,44] It might be possible that HGF stimulate these aberrant clones which otherwise would remain dormant.[45] This theory is supported by a study published by Kim *et al*. showing that pharmacological doses of G-CSF significantly increased aberrant clones carrying the monosomy 7 in patients with MDS.[46] Of note in our study, the rate of the development of PNH was higher in the HGF arm, although it did not reach statistical significance (Figure 5). Whether this is a true effect induced by the administration of HGF or part of the natural course of the disease itself, as reported previously, remains to be shown in larger scale series. An interesting finding in our systematic review was the lower relapse rate associated with the addition of HGF, which did not translate into better survival. This might be due to the high response rate (50-60%) in patients failing or relapsing after first-line treatment.[47,48] As for infections, the guidelines for the diagnosis and management of acquired aplastic anemia published in 2003 recommend considering the use of HGF in patients with severe systemic infections not responding to intravenous antibiotics or antifungals.[5] This issue was not in the frame of our review. Yet, we could not show the usefulness of HGF for prevention of clinically documented or severe infections despite their theoretical advantage in terms of neutrophil recovery acceleration.

Several limitations in our analysis merit consideration. First, the paucity of randomized controlled trials. Our search strategy yielded only six trials including 414 patients. Therefore, the power of our analysis is limited by the small number of trials and patients in each trial (minimum 27, maximum 102 patients in each trial). This is probably due to the rarity of this entity and the slow recruitment of patients to trials. A recent large EBMT trial addressing the issue of HGF has been prematurely closed due to slow recruitment and its results are still pending.[35] Results of this important trial might solve some of the issues raised in this meta-analysis. Although our inclusion criteria referred to all patients with acquired aplastic anemia, all but one trial included patients with severe or very severe aplastic anemia. Nevertheless, we could not perform a subgroup analysis by the severity of aplastic anemia. Various trials used different types of HGF. We could not conduct subgroup analyses for each type or dose because of scarcity of trials. Since it is well known that PNH and hypoplastic MDS might be misdiagnosed as aplastic anemia, another limitation of our study could be an overestimation of the rate of secondary clonal disorders such as MDS/AML or PNH, especially in the HGF arm, a bias that might also be influenced by the small number of patients in each arm. Finally, as shown in Table 1, different trials used various definitions for

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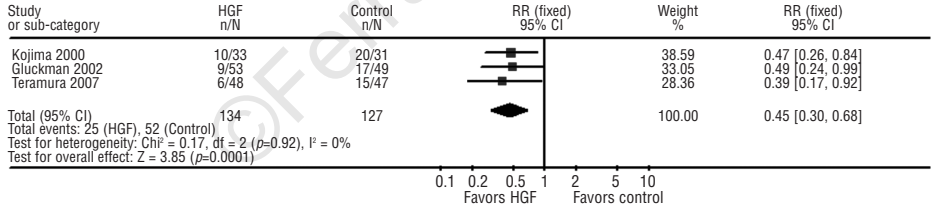

Figure 4. Risk for relapse comparing between patients treated with IST and HGF and those treated with IST and control.

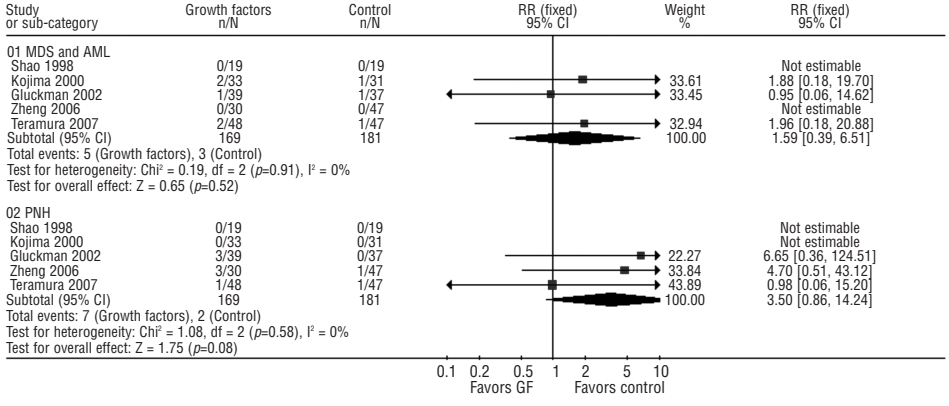

Figure 5. Risk for secondary clonal disorders: risk for MDS/AML and risk for PNH, comparing between patients treated with IST and HGF and those treated with IST and control.

the disease and response criteria, which could be a source for bias (i.e. better outcomes in studies using less stringent criteria). Thus, the most reliable parameter should be overall mortality.

In conclusion, our systematic review shows that according to the current evidence there is no role for the use of HGF in the treatment of severe aplastic anemia due to lack of effect on overall mortality, response rate, clinically documented and severe infections.

Future trials should further address these and other issues, including the role of HGF as supportive treatment for patients with severe or resistant bacterial and fungal infections and their role in patients with non-severe aplastic anemia not receiving IST.

Authorship and Disclosures

RG, AG-G, PR: conception and design, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, final approval; MP: design, interpretation of data, revising the article critically for important intellectual content, final approval; IB-B: conception and design, revising the article critically for important intellectual content, final approval; LV, MY: analysis and interpretation of data, revising the article critically for important intellectual content, final approval; OS: design, analysis and interpretation of data, revising the article critically for important intellectual content, final approval.

The authors reported no potential conflicts of interest.

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