Efficacy of palifermin on oral mucositis and acute GVHD after hematopoietic stem cell transplantation (HSCT) in hematology malignancy patients: a meta-analysis of trials

Aim of the study: Herein, this meta-analysis study evaluated the efficacy of palifermin after HSCT on the incidence and severity of OM or aGVHD in hematologic malignancy patients in randomized clinical trials (RCTs).

Materials and methods: To compare the efficacy of palifermin on adverse events, OM and aGVHD compared with placebo, we searched databases of PubMed/Medline, Web of Science and Cochrane Library for RCTs based on a number of criteria.

Results: There was no difference observed in the incidence of OM and aGVHD between two groups. The subgroup analysis didn't show significant differences in two groups for aGVHD grade 2–4 (odds ratio [OR] = 1.54, 95% confidence interval (CI): 0.70–3.39, p = 0.28), aGVHD grade 3–4 (OR = 0.97, 95% CI: 0.48–1.94, p = 0.92), OM grade 2–4 (OR = 0.76, 95% CI: 0.42–1.38, p = 0.37) and OM grade 3–4 (OR = 0.54, 95% CI: 0.25–1.15, p = 0.11], but erythema as an adverse effect in palifermin group was higher than placebo group (OR = 1.86, 95% CI: 1.10–3.15, p = 0.02].

Conclusions: This meta-analysis of six clinical trials found no statistically significant difference in OM and aGVHD grades in patients receiving 60 µg/kg/day dose of palifermin compared with those receiving a placebo. However, oral mucosal erythema was more prevalent among patients receiving palifermin than patients receiving a placebo.

Key words: palifermin, hematopoietic cell transplantation, hematology malignancy, adverse event, meta-analysis.

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Introduction

Hematopoietic stem cell transplantation (HSCT) is a potentially curative therapeutic procedure for patients with relapsed or refractory hematological malignancies (HMs) [1]. Mucositis is a major factor contributing to morbidity and mortality in patients undergoing HSCT, commonly developing after radiation-based conditioning regimens [2, 3]. The overall incidence of mucositis in HSCT is usually reported to be between 75 and 99% [4]. Oral mucositis (OM) remains one of the most significant complications of high-dose chemotherapy and HSCT [5]. The OM is an inflammation of the mucous that is characterized by color alteration, atrophy, ulceration, edema, and alteration of the local perfusion [6, 7]. Palifermin is a recombinant human keratinocyte growth factor (KGF) which is known to stimulate the growth of epithelial cells in a wide variety of tissues [8]. Palifermin has been shown as a cost-effective therapy in an analysis using the Spanish healthcare system [9]. In addition to, palifermin can affect on GVHD in the HM patients after HSCT [3]. The aim of this meta-analysis study was to assess the efficacy of palifermin after HSCT on the incidence and severity of OM or acute graft-versus-host disease (aGVHD) in HM patients in randomized clinical trials (RCTs).

Materials and methods

Search strategies

We conducted a comprehensive search with search terms included with palifermin and hematopoietic stem cell transplantation or HSCT or stem-cell transplant or stem cell transplant or hematopoietic cell transplantation or HCT or hematopoietic stem cell transplant or stem cell transplantation or stem-cell transplantation or hematopoietic stem-cell transplantation and oral mucositis or mucositis in databases of PubMed/Medline, Web of Sci-

ence and Cochrane Library from Jan 1991 to 24th Nov 2016 for English-language publications.

Study selection

Three authors evaluated the selection of the studies. The first author (M.S) conducted the search and applied the selection criteria and then M.R confirmed the selection from the overall search results. If there was any disagreement between the two authors, the third author (H.R.M) resolved the problem. All the articles of this study were examined for assessment of the efficacy of palifermin after HSCT in HM patients compared with placebo. Studies in this meta-analysis had to include the following inclusion criteria: a) the clinical trial with two arms (palifermin and placebo groups); b) the human studies; c) the comparison of GVHD and/or OM based on the World Health Organization (WHO) in two groups after HSCT; d) the studies reporting adverse events in two groups undergoing HSCT. Exclusion criteria: a) duplication of previous publications; b) the review, case report, case series, case-control and retrospective studies; c) the trial without placebo group; d) the trial without complete information about OM and/or GVHD; e) the trial reporting solid tumor.

Fig. 1. Flow diagram

Data extraction

The name of author, year of publication, country of the region, the number of patients in each palifermin group, the number of patients in each placebo group, the dose of palifermin and the type of HSCT was collected for each study that met our criteria. The incidence and severity of OM, aGVHD and adverse events included in the studies were reported. OM was assessed using the WHO toxicity scale. Adverse events were assessed during the study period and graded according to the WHO and National Cancer Institute Common Toxicity Criteria (NCI-CTC) toxicities scale. Severity of GVHD was determined clinically (physical examination and laboratory serum values), with biopsies of affected organs when available. Also, GVHD was graded weekly during the first 2 months after transplantation and then every other week to day 100 by specific observers according to consensus criteria that the study of Przepiorka et al. has used more descriptions [10].

Quality evaluation

Two authors (M.R and M.S) performed the quality of the studies using 13 criteria [11] that these selected criteria were based on the guideline described by Fowkes and Fulton [12] for evaluating meta-analysis study effectively and a control for influence bias.

Statistical analyses

Analyses of data (a random-effect model) were used by Review Manager 5.3 (RevMan 5.3, The Cochrane Collaboration, Oxford, United Kingdom) using odds ratio (OR) and 95% confidence intervals (CIs). The heterogeneity between estimations was calculated by the Q and I^2 statistics that for the Q statistic, heterogeneity was considered for $p < 0.1$. The I^2 statistic yields results ranging from 0 to 100% ($I^2 = 0–25\%$, no heterogeneity; $I^2 = 25–50\%$, moderate heterogeneity; $I^2 = 50–75\%$, large heterogeneity; $I^2 = 75–100\%$, extreme heterogeneity) [13]. The publication bias was evaluated through funnel plot analysis with the Begg's and Egger's tests. *P*-value (2-tailed) < 0.05 was considered in this meta-analysis statistically significant.

Results

Study characteristics

Out of 126 studies searched in databases, 39 studies were eligible for evaluation. Out of 33 studies, 6 trials reported the prevalence of GVHD and/or OM grades with adverse events in palifermin group compared with the placebo group after HSCT in HM patients that Fig. 1 shows the screening process of studies. The studies were reported between 2004 and 2016 that these 6 studies [14–19] included 419 patients in palifermin group and 316 patients in the placebo group (Table 1). The dose of palifermin was 60 µg/kg/day for all trials [15–19], except for one study [14] that doses were 40 µg/kg/day (cohort 1 only, 8 patients) or 60 µg/kg/day (all cohorts). Three studies [14, 16, 18] reported the results in HM, one study [15] evaluated multiple myeloma (MM) and two other studies [17, 19] assessed acute lymphoblastic leukemia (ALL) patients. Three studies
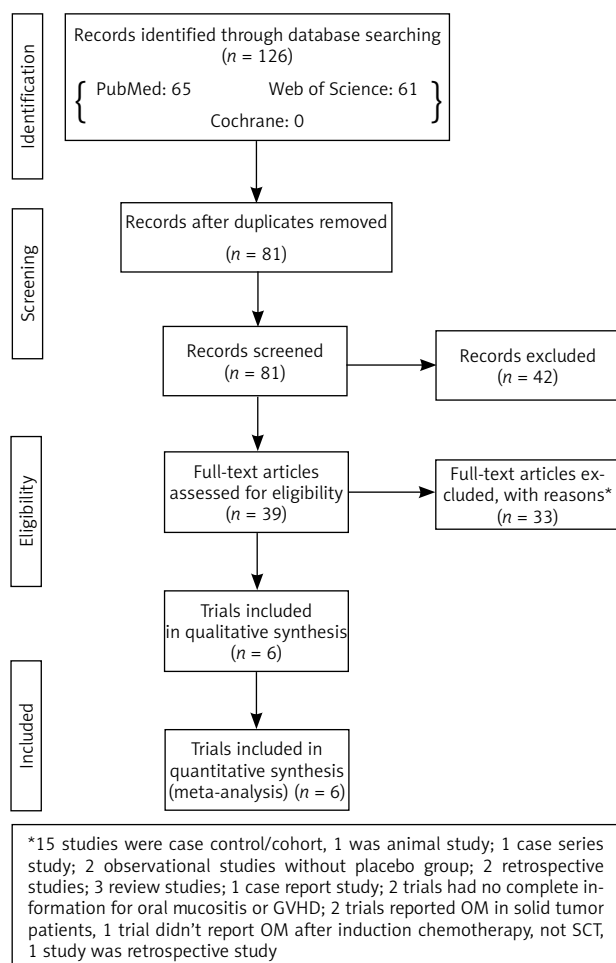
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Table 1. The characteristics of meta-analysis studies (*n* = 6)

Study (year)	Country	Cancer	Placebo Group (*N*)	Palifermin Group (*N*)	Type of SCT
Blazar *et al.* 2006 [14]	USA	HM	31	69	Allogeneic
Blijlevens *et al.* 2013 [15]	Netherlands	MM	57	224*	Autologous
Jagasia *et al.* 2012 [16]	USA	HM	73	78	Allogeneic
Lucchese *et al.* 2016 [17]	Italy	ALL	27	27	Autologous
Lucchese *et al.* 2016 [19]	Italy	ALL	22	24	Allogeneic
Spielberger *et al.* 2004 [18]	USA	HM	106	106	Autologous

*115 patients randomized to pre-/post- high-dose Melphalan (HDM) and 109 patients randomized to pre-HDM.
HM – hematologic malignancy; MM – multiple myeloma; SCT – stem cell transplant, ALL – acute lymphoblastic leukemia

Table 2. Qualitative scoring of the included articles (*n* = 6)

Component	Definition	Blazar *et al.* [14]	Blijlevens *et al.* [15]	Jagasia *et al.* [16]	Lucchese *et al.* [17]	Lucchese *et al.* [19]	Spielberger *et al.* [18]
1. Study design	Description of study design	E	E	E	E	E	E
2. Participants	Eligibility criteria for participants	E	E	E	E	E	E
	Entry criteria and exclusion	E	E	E	E	E	E
3. Interventions	Sufficient details	E	E	E	E	E	E
	Description of modifier effects	E	E	E	E	E	E
4. Outcomes	Completely defined	E	E	E	E	E	E
5. Sample size	How sample size was determined	NE	NE	NE	NE	NE	NE
6. Randomization	Method used	E	E	E	E	E	E
7. Blinding	Who was blinded and how	NE	NE	NE	E	E	NE
8. Control group acceptable	Definition of control	NE	NE	NE	P	P	P
9. Statistical methods	Statistical methods used	E	E	E	E	E	E
	Methods for additional analyses	E	E	E	E	E	E
10. Participant flow	For each group, losses and exclusions	E	E	E	E	E	E
11. Baseline data	Baseline clinical of each group	E	E	E	E	E	E
12. Numbers analyzed	For each group	E	E	E	E	E	E
13. Interpretation	Consistent with results	E	E	E	E	E	E

NE – not explained; E – explained; P – partially

[14, 16, 19] reported the results after allo-HSCT and three studies [15, 17, 18] after auto-HSCT. One study [15] reported a total of 224 patients (115 patients randomized to pre-/post-high-dose Melphalan (HDM) and 109 patients randomized to pre-HDM).

Meta-analysis results

The results of the pooled estimates of OM and aGVHD grades in two groups have been shown in Fig. 2. A random-effect model was used in all six trials. The subgroup analysis didn't show significant differences in two groups for aGVHD grade 2–4 (OR = 1.54, 95% CI: 0.70–3.39, *p* = 0.28), aGVHD grade 3–4 (OR = 0.97, 95% CI: 0.48–1.94, *p* = 0.92), OM grade 2–4 (OR = 0.76, 95% CI: 0.42–1.38, *p* = 0.37) and OM grade 3–4 (OR = 0.54, 95% CI: 0.25–1.15, *p* = 0.11). Also, heterogeneity for subgroups of aGVHD grade 2–4, OM grade 2–4 and OM grade 3–4 was moderate, large and extreme, respectively, but there was no heterogeneity for aGVHD grade 3–4.

The results of the pooled estimates of the prevalence of adverse events after HSCT have been shown in Fig. 3. The total analysis showed that there was a significant difference between two groups in total adverse events (OR = 1.15, 95% CI: 0.92–1.44, *p* = 0.20) with large heterogeneity. The subgroup analysis showed that there were no significant differences between two groups for edema (OR = 1.28, 95% CI: 0.80–2.05, *p* = 0.31), rash (OR = 1.23, 95% CI: 0.67–2.25, *p* = 0.50], infection (OR = 0.45, 95% CI: 0.06–3.48, *p* = 0.44), febrile neutropenia (OR=0.81, 95% CI: 0.40–1.62, *p* = 0.55), total parenteral nutrition (OR = 1.09, 95% CI: 0.49–2.43, *p* = 0.83), cough (OR = 1.23, 95% CI: 0.80–1.88, *p* = 0.35), pruritus (OR = 0.75, 95% CI: 0.28–2.00, *p* = 0.57), taste alteration (OR = 1.01, 95% CI: 0.30–3.36, *p* = 0.99), white film coating tongue and mouth (OR = 1.91, 95% CI: 1.00–3.64, *p* = 0.05), sensation of increased tongue thickness (OR = 1.72, 95% CI: 0.80–3.69, *p* = 0.16), taste loss (OR = 1.28, 95% CI: 0.41–4.01, *p* = 0.67) and paresthesia (OR = 3.45, 95% CI: 0.79–15.14, *p* = 0.10), but there was a signifi-

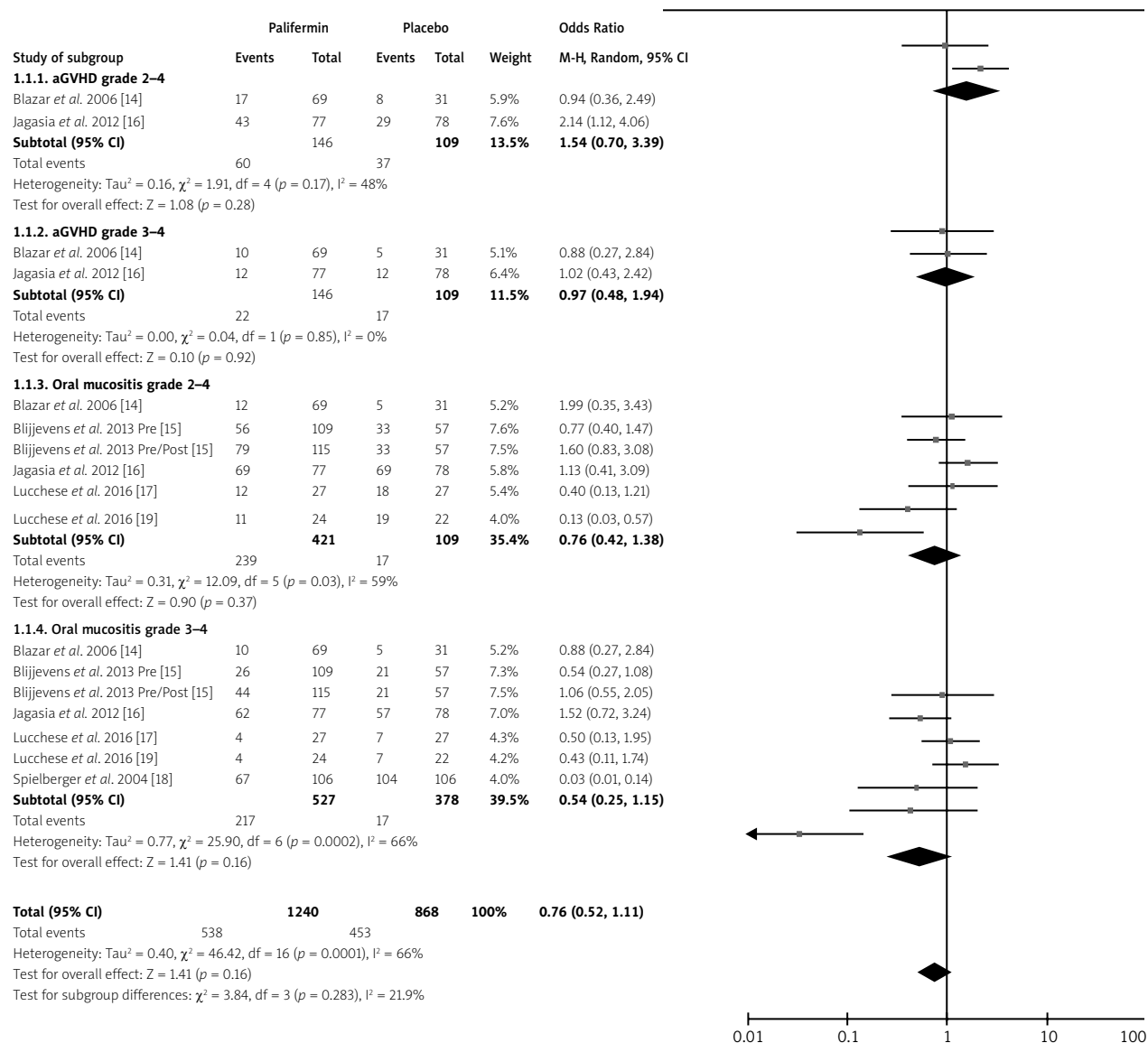| Study of subgroup	Palifermin Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1. aGVHD grade 2–4						
Blazar *et al.* 2006 [14]	17	69	8	31	5.9%	0.94 (0.36, 2.49)
Jagasia *et al.* 2012 [16]	43	77	29	78	7.6%	2.14 (1.12, 4.06)
Subtotal (95% CI)		146		109	13.5%	1.54 (0.70, 3.39)
Total events	60		37			
Heterogeneity: Tau² = 0.16, χ² = 1.91, df = 4 (p = 0.17), I² = 48%						
Test for overall effect: Z = 1.08 (p = 0.28)						
1.1.2. aGVHD grade 3–4						
Blazar *et al.* 2006 [14]	10	69	5	31	5.1%	0.88 (0.27, 2.84)
Jagasia *et al.* 2012 [16]	12	77	12	78	6.4%	1.02 (0.43, 2.42)
Subtotal (95% CI)		146		109	11.5%	0.97 (0.48, 1.94)
Total events	22		17			
Heterogeneity: Tau² = 0.00, χ² = 0.04, df = 1 (p = 0.85), I² = 0%						
Test for overall effect: Z = 0.10 (p = 0.92)						
1.1.3. Oral mucositis grade 2–4						
Blazar *et al.* 2006 [14]	12	69	5	31	5.2%	1.99 (0.35, 3.43)
Blijjevens *et al.* 2013 Pre [15]	56	109	33	57	7.6%	0.77 (0.40, 1.47)
Blijjevens *et al.* 2013 Pre/Post [15]	79	115	33	57	7.5%	1.60 (0.83, 3.08)
Jagasia *et al.* 2012 [16]	69	77	69	78	5.8%	1.13 (0.41, 3.09)
Lucchese *et al.* 2016 [17]	12	27	18	27	5.4%	0.40 (0.13, 1.21)
Lucchese *et al.* 2016 [19]	11	24	19	22	4.0%	0.13 (0.03, 0.57)
Subtotal (95% CI)		421		109	35.4%	0.76 (0.42, 1.38)
Total events	239		17			
Heterogeneity: Tau² = 0.31, χ² = 12.09, df = 5 (p = 0.03), I² = 59%						
Test for overall effect: Z = 0.90 (p = 0.37)						
1.1.4. Oral mucositis grade 3–4						
Blazar *et al.* 2006 [14]	10	69	5	31	5.2%	0.88 (0.27, 2.84)
Blijjevens *et al.* 2013 Pre [15]	26	109	21	57	7.3%	0.54 (0.27, 1.08)
Blijjevens *et al.* 2013 Pre/Post [15]	44	115	21	57	7.5%	1.06 (0.55, 2.05)
Jagasia *et al.* 2012 [16]	62	77	57	78	7.0%	1.52 (0.72, 3.24)
Lucchese *et al.* 2016 [17]	4	27	7	27	4.3%	0.50 (0.13, 1.95)
Lucchese *et al.* 2016 [19]	4	24	7	22	4.2%	0.43 (0.11, 1.74)
Spielberger *et al.* 2004 [18]	67	106	104	106	4.0%	0.03 (0.01, 0.14)
Subtotal (95% CI)		527		378	39.5%	0.54 (0.25, 1.15)
Total events	217		17			
Heterogeneity: Tau² = 0.77, χ² = 25.90, df = 6 (p = 0.0002), I² = 66%						
Test for overall effect: Z = 1.41 (p = 0.16)						
Total (95% CI)		1240		868	100%	0.76 (0.52, 1.11)
Total events	538		453			
Heterogeneity: Tau² = 0.40, χ² = 46.42, df = 16 (p = 0.0001), I² = 66%						
Test for overall effect: Z = 1.41 (p = 0.16)						
Test for subgroup differences: χ² = 3.84, df = 3 (p = 0.283), I² = 21.9%						

0.01 0.1 1 10 100

Fig. 2. Forest plot of oral mucositis and acute GVHD grades

cant difference for erythema (OR = 1.86, 95% CI: 1.10–3.15, p = 0.02). The subgroup heterogeneity for adverse events is demonstrated in Fig. 3.

Quality evaluation

Table 2 shows the qualitative scoring of the included articles in meta-analysis. All studies [14–19] described the use of randomization, but none of them completely reported the sample size calculation. Two studies [17, 19] explained blinding. Three studies [14–16] describe fully the definition of controls, but three studies [17–19] partially.

Publication bias

The funnel plot analysis of random-effect of the studies in this meta-analysis has been shown in Fig. 4. The results of the Begg's and Egger's tests revealed that no publication biases existed in terms of OM grade 2–4, OM grade 3–4 (Fig. 4A), infection, edema, rash, febrile neutropenia,

total parenteral nutrition, cough, erythema, pruritus, white film coating tongue or mouth, sensation of increased tongue thickness and paresthesia (Fig. 4B). Regarding aGVHD grade 2–4, aGVHD grade 3–4 (Fig. 4A), Begg's and Egger's tests revealed no publication biases and could not be performed because only two studies were included. Regarding taste alteration and taste loss (Fig. 4B), a Begg's test revealed no publication bias, but an Egger's test revealed significant publication bias.

Discussion

This meta-analysis study evaluated OM, aGVHD and adverse events after HSCT in the patients undergoing palifermin compared with placebo. The results showed that palifermin had no effect on the incidence of OM and aGVHD. Although only the prevalence of erythema was significantly more in palifermin group, totally the incidence of the adverse events was significantly more in palifermin group compared with placebo. The common side events,
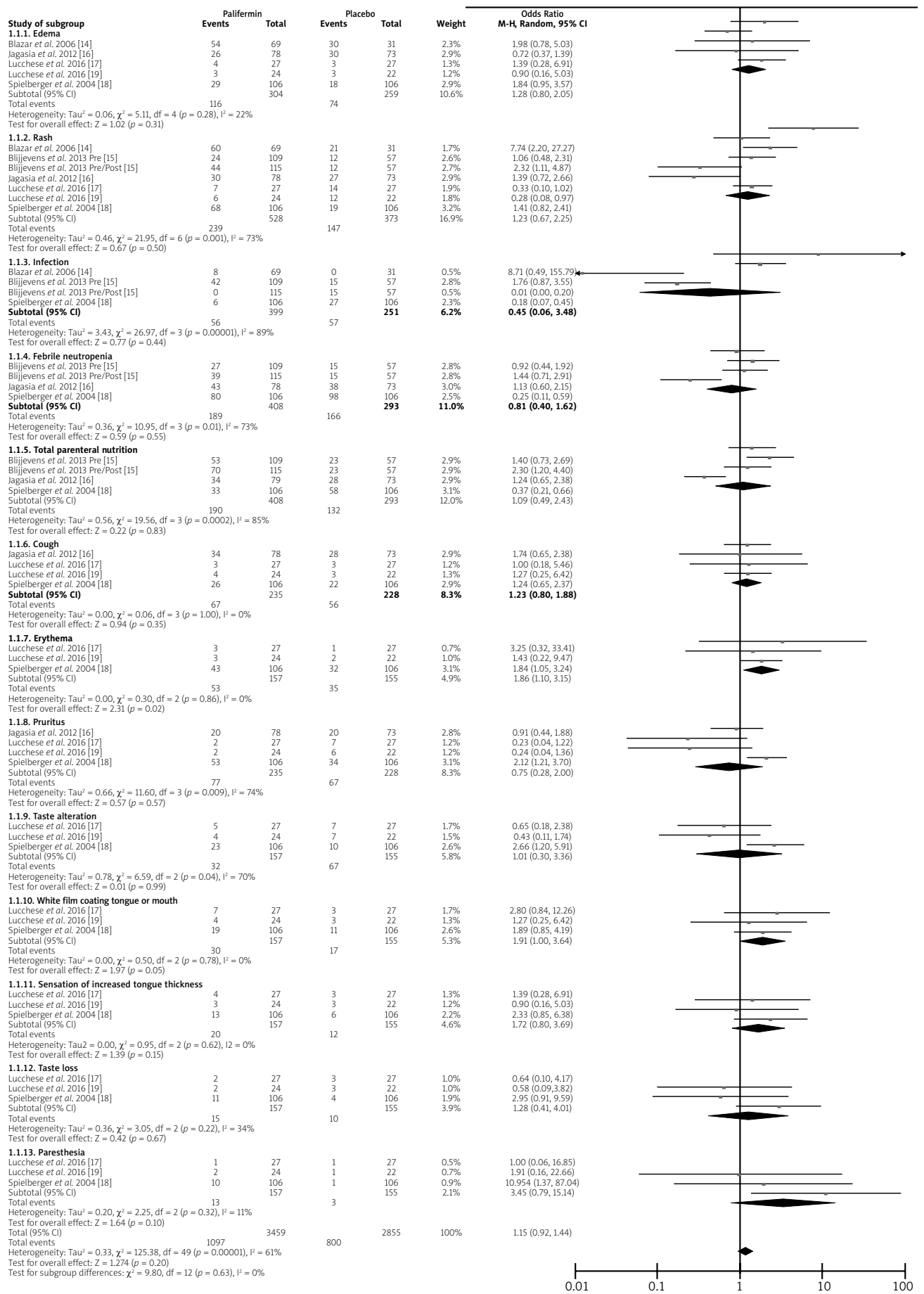
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Fig. 3. Forest plot of the prevalence of adverse events after HSCT
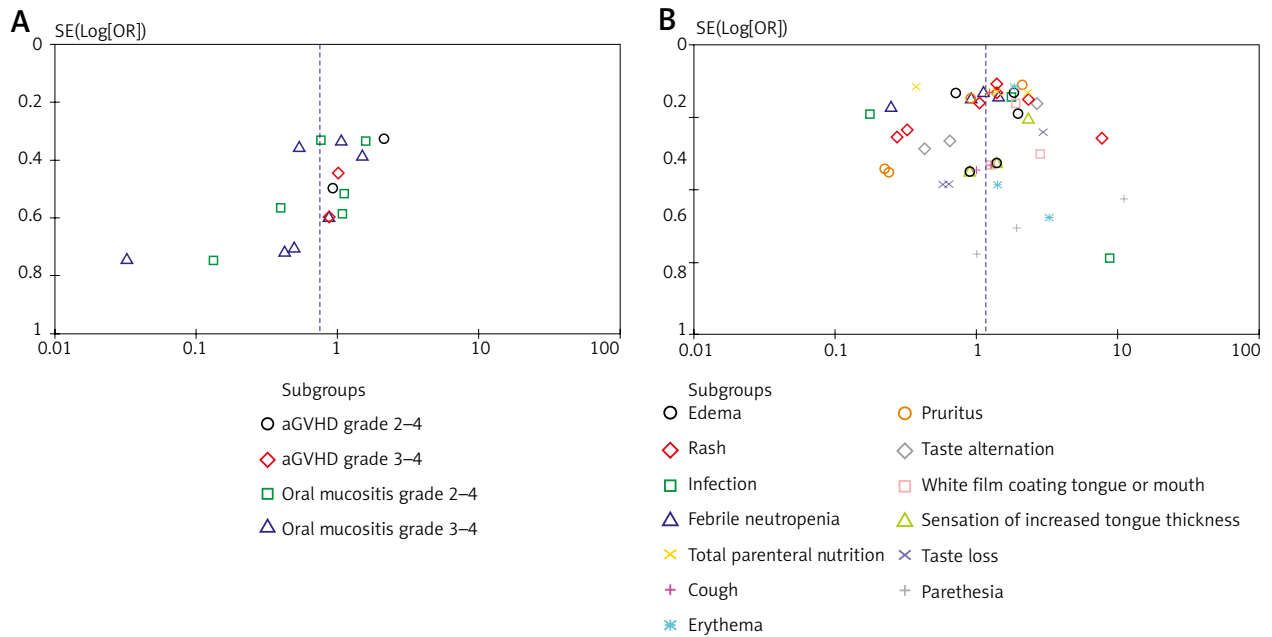
Fig. 4. The funnel plot of (**A**) oral mucositis and acute GVHD grades, (**B**) the prevalence of adverse events after HSCT

which have been noted with palifermin included a white coating of the tongue, rash, edema and elevated amylase and lipase [18–22], whereas this study showed that erythema can be an another common side event from palifermin.

The efficacy of palifermin has been established in a number of clinical trials, in which it was shown to reduce significantly the duration, incidence, and severity of OM after intensive chemotherapy and radiotherapy for HMs [23]. The results showed that in patients with hematologic cancers who were undergoing auto-HSCT after total-body irradiation (TBI) and high-dose chemotherapy, the incidence of grade 4 OM was more significantly reduced with palifermin than with placebo and also the incidence of grade 3–4 OM was 98% in the control group versus 63% in the palifermin group [18]. A retrospective study on 251 patients undergoing allo-HSCT that 154 of whom received peritransplant palifermin, the efficacy of palifermin was only significant in patients who received a TBI-, but not busulfan-based chemotherapy conditioning regimen and also the results showed that palifermin did not effect on GVHD [24]. One RCT study [16] evaluated the efficacy of palifermin after myeloablation and allo-HSCT. One group received palifermin 60 µg/kg/day for three consecutive days before conditioning and a single dose of 180 mg/kg after TBI and another group received methotrexate (plus cyclosporine A or tacrolimus). The incidence and severity of aGVHD were similar between treatment groups compared to placebo groups. The most commonly reported treatment-related adverse events were rash, pruritus and erythema. Another RCT study [14], investigated various dosing regimens of palifermin in allo-HSCT and concluded there were no significant differences in the incidence and severity of aGVHD between the palifermin and placebo groups, but palifermin was associated with reduced incidence and severity of mucositis (measured three times weekly), but only in patients conditioned with fractionated TBI-based regimens. Therefore, palifermin protection from

lethality and organ tissue injury varies with the conditioning regimen and intensity [25] and it is important that palifermin given prior to TBI-based regimens in rodents improved thymopoiesis and peripheral immune reconstitution, likely via effects on thymic epithelial cells [26, 27].

The case-control study of Nasilowska-Adamska *et al*. [28] evaluated the role of palifermin in the prevention during auto- or allo-HSCT and after conditioning regimens. A significant reduction was noted in the incidence of OM and aGVHD in the palifermin group compared to the control group [28]. Langner *et al*. [29] reported the incidence of grades 2–4 OM was significantly less than the control group, whereas in grades 3–4 was not significant between two groups and palifermin had no effect on the incidence and severity of aGVHD. One RCT study checked the efficacy of palifermin in acute lymphoblastic leukemia pediatric patients. During auto-HSCT therapy, patients in the palifermin group were randomly assigned to receive palifermin, 60 µg/kg/day, intravenously as a single dose 3 days before auto-HSCT infusion. There was a statistically significant reduction in the incidence of grade 3–4 OM in the palifermin group compared with the control group [17]. In a high-dose melphalan setting after auto-HSCT, palifermin was unable to reduce OM in MM transplant patients [15].

The trials showed the benefits of palifermin after HSCT in patients with HMs that received TBI-based conditioning regimens, but didn't show for the patients receiving non-TBI based regimens. The meta-analysis showed that a dose of 60 µg/kg/day of palifermin can't be effective in all patients and the clinicians should pay attention to the types of HSCT, regimen, and malignancy in the patients undergoing palifermin therapy. Also, the higher incidence and severity of OM or aGVHD and also differences in the prevalence of adverse events in some RCTs may be due to the difference in conditioning regimens or HSCT used or type of HM. Limitations of this meta-analysis were: 1) The adverse events reported in the studies after HSCT were

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not similar. 2) All studies didn't report the incidence and severity of all aGVHD or OM grades. 3) Type of chemotherapy and type of HSCT were different in the studies. 4) One study used two doses of palifermin in the patients. 5) One study did palifermin therapy in two types of courses (pre-/post-HDM and pre-HDM).

In conclusion, this meta-analysis of six clinical trials found no statistically a significant difference in OM and aGVHD grades in patients receiving 60 μg/kg/day dose of palifermin compared with those receiving a placebo. However, oral mucosal erythema was more prevalent among patients receiving palifermin than patients receiving a placebo.

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The authors declare no conflict of interest.

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