



The impact of RAGE inhibition in animal models of bacterial sepsis: a systematic review and meta-analysis

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Abstract

Objective: To evaluate the impact of inhibition of the receptor for advanced glycation end products (RAGE) on the outcome of bacterial sepsis in animal models.

Methods: Relevant publications were identified by systematic searches of PubMed, ISI Web of Science and Elsevier-Scopus databases.

Results: A total of Eleven studies with moderate quality were selected for analysis. A meta-analysis of survival rates revealed a significant advantage of RAGE inhibition in comparison with controls (HR 0.67, 95% CI 0.52–0.86). This effect was most pronounced in polymicrobial infection (HR 0.28, 95% CI 0.14–0.55), followed by Gram positive (G^+) bacterial infection (HR 0.70, 95% CI 0.50–0.97) and Gram negative (G^-) bacterial infection (HR 0.89, 95% CI 0.58–1.38). For G^+ bacterial infection, RAGE inhibition decreased bacterial outgrowth and dissemination, inflammatory cell influx, plasma cytokine levels, and pulmonary injury.

Conclusions: RAGE inhibition appears to have a beneficial impact on the outcome of sepsis in animal models, although there are discrepancies between different types of infection.

Keywords

Receptor for advanced glycation end products, sepsis, systematic review, meta-analysis

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Introduction

Sepsis is a profoundly damaging and life-threatening condition in clinical practice. Although its true incidence remains unknown, conservative estimates suggest that sepsis is a leading cause of mortality and critical illness worldwide. Moreover, with the increased prevalence of antibiotic resistance, aging populations with more

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comorbidities, and the wider use of immunosuppressive therapies, the burden of this disease is expected to grow.¹ According to the published guidelines of the Surviving Sepsis Campaign, sepsis is defined as a life-threatening organ dysfunction that is caused by dysregulation of host responses to infection. Septic shock is a subset of sepsis in which there is circulatory, cellular and metabolic dysfunction, and is associated with a higher risk of mortality.²

Understanding the pathophysiology of sepsis is an important first step in improving outcomes. Despite prioritization of sepsis research over the past two decades, the precise inflammatory dynamics of sepsis are still not completely understood, and innovations in the management of sepsis have been slow to appear. Consequently, there is an urgent need to further investigate the underlying pathophysiology of sepsis, and to develop new treatment strategies.

The receptor for advanced glycation end products (RAGE) is a member of the immunoglobulin superfamily. This superfamily engages numerous ligands and exhibits expression on many cells types.³ Previous studies have demonstrated that RAGE is a critical component of the deleterious effects of acute inflammatory disorders, including sepsis. Binding of ligands to RAGE can trigger several intracellular signaling cascades, leading to translocation of NF- κ B. In turn, NF- κ B induces RAGE expression in a positive feedback loop. This leads to amplification of pro-inflammatory signaling, sustained cellular inflammation, cellular dysfunction and tissue damage.⁴ Consequently, RAGE might be a promising target for sepsis control strategies.

Inhibition of RAGE expression or activity has been found to reduce inflammatory responses in several animal models, including models of diabetic atherosclerosis, delayed-type hypersensitivity and collagen-induced arthritis.⁵ However, it has not yet been determined whether RAGE inhibition

is beneficial in sepsis, as previous studies have yielded conflicting results. Several studies have suggested that RAGE inhibition attenuates the systematic inflammatory response and ensuing organ damage.^{3,4} Other studies have showed that RAGE inhibition causes an enhanced outgrowth of bacterial flora at the primary site of infection, together with increased spread to distant body compartments.^{5,6} To address these discrepancies, we performed a systematic review and meta-analysis to evaluate the impact of RAGE inhibition on the outcome of sepsis in animal models.

Materials and methods

Literature search

The literature included in our analysis was selected from PubMed, ISI Web of Science and Elsevier-Scopus databases in April 2017. The search terms “receptor for advanced glycation end product” or “RAGE” were used in combination with words related to sepsis, namely “sepsis”, “septic”, “bacterial infection” or “bacteremia”. We also manually extended our search to include the bibliographic reference lists of the research articles included in our study and relevant review articles.

Eligible studies and data extraction

Eligible studies had to meet all the following criteria: (1) *in vivo* controlled studies using an animal model with a sepsis challenge; (2) the intervention group was homozygous RAGE knockouts (RAGE^{-/-}), RAGE heterozygotes (RAGE^{+/-}) or wild-type (WT) animals treated with anti-RAGE antibodies; (3) sepsis was induced by bacterial infection; and (4) the article was published in English. The major reasons for exclusion of studies were: (1) other methods of RAGE inhibition were used, such as administration of soluble RAGE (sRAGE), that not only block the RAGE pathway, but also other pathways

related to sepsis, such as toll-like receptor pathways; (2) the data were overlapping; and (3) full texts of the publications were not available.

Two authors (Zhao X and Liao YN) independently extracted the data from all eligible studies, including the first author, publication year, country, RAGE inhibition method, method of sepsis induction, infection type, antibiotics applied and basic experimental animal information. Discrepancies between the two authors in terms of study inclusion and data extraction were resolved by discussion among all authors.

Quality assessments of included studies

A checklist modified from the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) was used to assess the methodological quality of the included studies.⁷ One point was tallied for written evidence of each of the following criteria: peer-reviewed publication, randomization of subjects into treatment groups, blind assessment of outcomes, monitoring of physiological parameters such as blood pressure, calculation of the sample size necessary to achieve sufficient power, statement of compliance with animal welfare regulations, avoidance of anesthetic agents related to outcome of sepsis, statement of potential conflicts of interest, and use of a suitable animal model.

Statistical methods

If appropriate comparisons between the RAGE inhibition group and control group were available for a selected study, a meta-analysis was conducted. Otherwise, a descriptive review of the identified evidence was carried out. For the survival rate, a hazard ratio (HR) is recommended as the most appropriate statistic because it allows

for differences in sample size and time to an event. However, no study reported HR directly, so an alternative method for extracting summary statistics from survival curves was used for the meta-analysis of time-to-event outcomes.⁸ We also conducted a subgroup analysis for three different microbial infection types: polymicrobial infection, Gram positive (G^+) or Gram negative (G^-). A P -value less than 0.05 was considered statistically significant. Statistical analysis was performed using the Review Manager (RevMan5.3) package provided by the Cochrane Library.

Results

Descriptions of the included studies

The comprehensive search strategy on the impact of RAGE inhibition on sepsis in animal models resulted in 852 records. After duplicates were removed, 376 studies remained. After title and abstract screening, 32 full-text studies were screened. Ultimately, 11 studies were included in our systematic review and meta-analysis (Figure 1).^{9–19} Lutterloh et al.¹⁰ investigated the effects of RAGE^{-/-}, RAGE^{+/-}, and anti-RAGE antibody administration on sepsis separately; these experiments were treated as three separate studies. Ramsgaard et al.¹³ and Achouiti et al.¹⁸ also used lipopolysaccharide (LPS) to induce sepsis to examine RAGE inhibition. These results were also included in this analysis.

The characteristics of all included studies are summarized in Table 1. These characteristics varied considerably between the studies, particularly the method used to induce sepsis. Three studies used *Escherichia coli*, two studies used cecal ligation and puncture (CLP), two studies used *Streptococcus pneumoniae*, two studies used *Staphylococcus aureus*, two studies used LPS in additional experiments, one study used *Klebsiella pneumoniae*, and the remaining study used *Acinetobacter baumannii*.

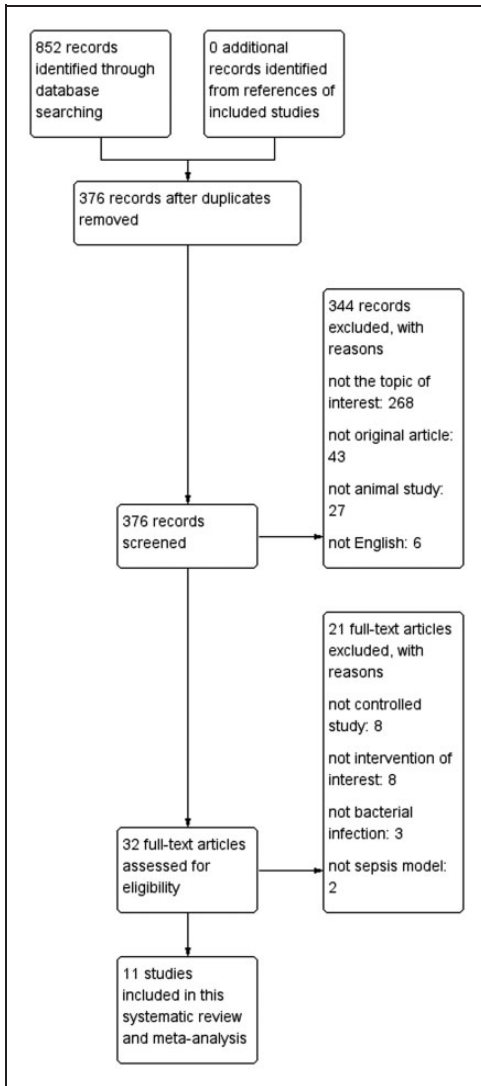


Figure 1. Flow diagram showing literature search and selection results.

Methodological quality of included studies

Overall, the quality score for the eleven included studies was moderate (mean 5.3), with scores ranging from 5 to 7. No study described the randomization of animals into treatment groups, nor the sample size calculation to achieve sufficient power.

Only one study reported monitoring of physiological parameters, and only two studies stated that the outcome measures were assessed by experimenters who were blind to the treatment condition (Table 2).

Overall analysis of survival rate

Six of the studies presented Kaplan-Meier survival curves comparing the RAGE inhibition group and the control group following sepsis.^{9–11,15,18,19} The data extracted from the survival curves is summarized in Table 3. Meta-analysis of these studies revealed that the RAGE inhibition group had a significantly higher survival rate than the control group (HR 0.67, 95% CI 0.52–0.86, $P=0.001$). Heterogeneity for this outcome was moderate ($P=0.10$, $I^2=42\%$; Figure 2).

Subgroup analysis of survival rate

We conducted a subgroup analysis per infectious type. For polymicrobial infection, meta-analysis of two studies (including five experiments)^{9,10} revealed that RAGE inhibition had a significant survival benefit over the control (HR 0.28, 95% CI 0.14–0.55, $P=0.0002$). No statistical heterogeneity was found for this outcome ($I^2=0\%$, $P=0.71$). For G^+ bacterial infection, meta-analysis of two studies^{11,15} also demonstrated a significant survival benefit for RAGE inhibition over the control (HR 0.70, 95% CI 0.50–0.97, $P=0.03$), and moderate statistical heterogeneity was found for this outcome ($I^2=28\%$; $P=0.24$). For G^- bacterial infection, meta-analysis of two studies^{18,19} revealed that RAGE inhibition had a higher survival rate than the control, although the difference was not statistically significant (HR 0.89, 95% CI 0.58–1.38, $P=0.60$; Figure 2). Moderate statistical heterogeneity was found for this outcome ($I^2=21\%$; $P=0.26$).

Table 1. Characteristics of the included studies.

Authors	Year	Country	Strain/Species	Gender	Age	RAGE inhibition	Sepsis induction method	Bacterial dose	Infection type	Antibiotics applied
Lilieniek et al. ⁹	2004	Germany	C57BL/6 mice	NM	NM	RAGE ^{-/-}	CLP	-	Polymicrobial	None
Lutterloh et al. (RAGE ^{+/-}) ¹⁰	2007	America	I29SvEvBrd mice	Male	2-6 months	RAGE ^{-/-}	CLP	-	Polymicrobial	Trovafoxacin
Lutterloh et al. (RAGE ^{+/-}) ¹⁰	2007	America	I29SvEvBrd mice	Male	2-6 months	RAGE ^{+/-}	CLP	-	Polymicrobial	Trovafoxacin
Lutterloh et al. (antibody) ¹⁰	2007	America	I29SvEvBrd mice	Male	2-6 months	antibody	CLP	-	Polymicrobial	Trovafoxacin
van Zoelen et al. ¹¹	2009	Netherlands	C57BL/6 mice	NM	NM	RAGE ^{-/-}	Intranasal inoculation with <i>S. pneumoniae</i>	5 × 10 ⁵	Gram ⁺ bacteria	None
van Zoelen et al. ¹²	2009	Netherlands	C57BL/6 mice	Female	8-10 weeks	RAGE ^{-/-}	Intraperitoneal administration of <i>E. coli</i>	NM	Gram ⁻ bacteria	None
Ramsgaard et al. ¹³	2011	America	C57BL/6 mice	Male	NM	RAGE ^{-/-}	Intratracheal instillation of <i>E. coli</i>	1 × 10 ⁶	Gram ⁻ bacteria	None
Ramsgaard et al. (LPS) ¹³	2011	America	C57BL/6 mice	Male	NM	RAGE ^{-/-}	Intratracheal instillation of LPS	75 µg	LPS	None
Tadie et al. ¹⁴	2011	America	C57BL/6 mice	Male	8-10 weeks	RAGE ^{-/-}	Intraperitoneal administration of <i>E. coli</i>	1 × 10 ⁶	Gram ⁻ bacteria	None
Achouiti et al. ¹⁵	2013	Netherlands	C57BL/6 mice	NM	NM	RAGE ^{-/-}	Intravenous injection with <i>S. pneumoniae</i>	1 × 10 ⁶	Gram ⁺ bacteria	None
Achouiti et al. ¹⁶	2013	Netherlands	C57BL/6 mice	NM	NM	RAGE ^{-/-}	Intranasal inoculation with <i>S. aureus</i>	5 × 10 ⁵	Gram ⁺ bacteria	None
Achouiti et al. ¹⁷	2015	Netherlands	C57BL/6 mice	NM	NM	RAGE ^{-/-}	Subcutaneous injection with <i>S. aureus</i>	1 × 10 ⁵	Gram ⁺ bacteria	None
Achouiti et al. ¹⁸	2016	Netherlands	C57BL/6 mice	Male	10 weeks	RAGE ^{-/-}	Intranasal inoculation with <i>K. pneumoniae</i>	1 × 10 ⁴	Gram ⁻ bacteria	None
Achouiti et al. (LPS) ¹⁸	2016	Netherlands	C57BL/6 mice	Male	10 weeks	RAGE ^{-/-}	Intranasal inoculation with LPS	NM	LPS	None
Noro et al. ¹⁹	2017	America	C57BL/6 mice	Female	8 weeks	RAGE ^{-/-}	Retro-orbital inoculation with <i>A. baumannii</i>	9 × 10 ⁸	Gram ⁻ bacteria	None

NM: not mentioned; RAGE^{-/-}: homozygous RAGE knockouts; RAGE^{+/-}: RAGE heterozygotes; CLP: cecal ligation and puncture; *S. pneumoniae*: streptococcus pneumoniae; *E. coli*: *Escherichia coli*; LPS: lipopolysaccharide; *S. aureus*: *Staphylococcus aureus*; *K. pneumoniae*: *Klebsiella pneumoniae*; *A. baumannii*: *Acinetobacter baumannii*.

Table 2. Methodological quality of the included studies.

Study	1	2	3	4	5	6	7	8	9	Quality score
Liliensiek et al. ⁹	✓		✓	✓		✓	✓	✓	✓	7
Lutterloh et al. ¹⁰	✓		✓			✓	✓	✓	✓	6
van Zoelen et al. ¹¹	✓					✓	✓	✓	✓	5
van Zoelen et al. ¹²	✓					✓	✓	✓	✓	5
Ramsgaard et al. ¹³	✓					✓	✓	✓	✓	5
Tadie et al. ¹⁴	✓					✓	✓	✓	✓	5
Achouiti et al. ¹⁵	✓					✓	✓	✓	✓	5
Achouiti et al. ¹⁶	✓					✓	✓	✓	✓	5
Achouiti et al. ¹⁷	✓					✓	✓	✓	✓	5
Achouiti et al. ¹⁸	✓					✓	✓	✓	✓	5
Noto et al. ¹⁹	✓					✓	✓	✓	✓	5

1: peer-reviewed publication; 2: randomization of subjects into treatment groups; 3: blind assessment of outcomes; 4: monitoring of physiological parameters; 5: calculation of the sample size necessary to achieve sufficient power; 6: statement of compliance with animal welfare regulations; 7: avoidance of anesthetic agents related to outcome of sepsis; 8: statement of potential conflicts of interest; 9: use of a suitable animal model.

Table 3. Survival rates between the RAGE inhibition and control groups in the included studies.

Study	Sample size	Event	7-day survival rate	P value	O-E	V	HR
Liliensiek et al. ⁹	21 vs 25	4 vs 20	81% vs 20%	0.001	-6.20	3.72	0.19
Lutterloh et al. (RAGE ^{-/-}) ¹⁰	15 vs 15	3 vs 10	80% vs 33.3%	<0.001	-1.40	1.52	0.40
Lutterloh et al. (RAGE ^{+/-}) ¹⁰	23 vs 15	7 vs 10	69.6% vs 33.3%	<0.001	-1.98	1.47	0.26
Lutterloh et al. (antibody) ¹⁰	15 vs 15	7 vs 10	73.3% vs 33.3%	<0.001	-1.07	1.63	0.52
van Zoelen et al. ¹¹	15 vs 15	13 vs 15	13.3% vs 0	<0.01	-10.42	19.46	0.59
Achouiti et al. ¹⁵	8 vs 8	6 vs 7	25% vs 12.5%	>0.05	-2.04	15.27	0.87
Achouiti et al. ¹⁸	14 vs 14	12 vs 7	14.3% vs 50%	<0.05	1.53	3.72	1.51
Noto et al. ¹⁹	21 vs 21	12 vs 18	42.9% vs 14.2%	<0.005	-3.87	16.53	0.79

HR: hazard ratio; V: reciprocal of the variance of ln(HR) for time; O-E: ln(HR) divided by its variance for time; RAGE^{-/-}: homozygous RAGE knockouts; RAGE^{+/-}: RAGE heterozygotes.

Bacterial outgrowth and dissemination

Nine studies described the impact of RAGE inhibition on bacterial outgrowth or dissemination during sepsis. For polymicrobial infection, Lutterloh et al.¹⁰ showed that there were no significant differences in tissue colony counts in liver, spleen and peritoneal tissue between the RAGE

inhibition group (including the RAGE^{-/-}, RAGE^{+/-} and anti-RAGE antibody administration groups) and the control group. For G⁺ bacterial infection, although van Zoelen et al.¹¹ and two studies by Achouiti et al. found that RAGE inhibition reduced bacterial outgrowth or dissemination to distant organs, another study by Achouiti et al. did not observe this effect.¹⁵⁻¹⁷ For G⁻ bacterial

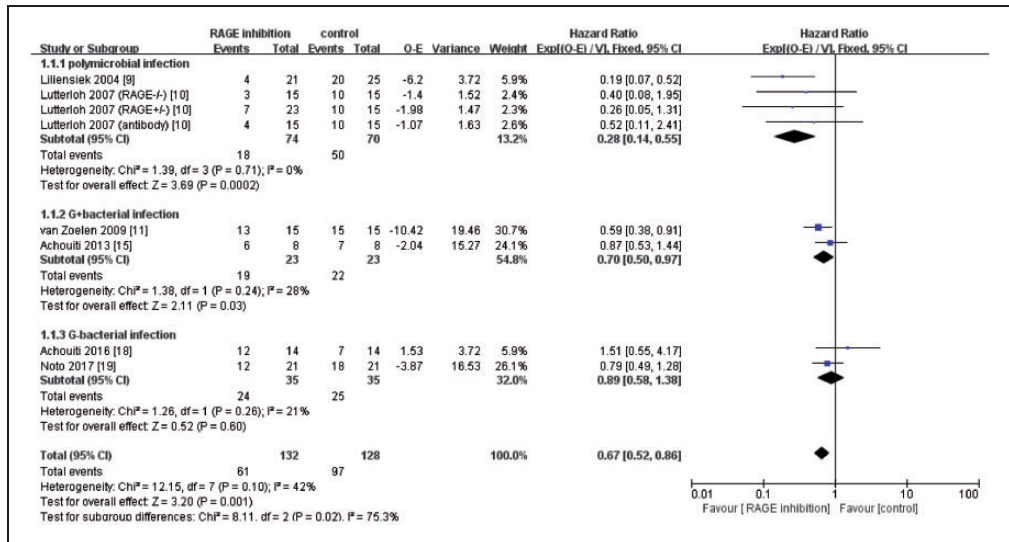


Figure 2. Meta-analysis of survival rates.

infection, van Zoelen et al.¹², Tadie et al.¹⁴ and Achouiti et al. all found that RAGE inhibition promoted bacterial outgrowth or dissemination. However, Noto et al. found that RAGE^{-/-} mice had significantly reduced bacterial burdens in comparison with WT mice.^{18,19}

Inflammatory cell influx

Nine studies investigated the impact of RAGE inhibition on inflammatory cell influx during sepsis. For polymicrobial infection, Liliensiek et al. found reduced numbers of inflammatory cells adherent to the peritoneum of the RAGE^{-/-} group compared with that of the WT group.⁹ For G⁺ bacterial infection, van Zoelen et al.¹¹ and one study from Achouiti et al. found a decreased influx of inflammatory cells in the RAGE^{-/-} group compared with the WT group. However, another study from Achouiti et al. did not show this alteration.^{15,16} For G⁻ bacterial infection, although Ramagaard et al. found significantly decreased inflammatory cell counts in

the RAGE^{-/-} group compared with the WT group, van Zoelen et al.¹², Tadie et al., Achouiti et al. and Noto et al. did not observe such a difference.^{13,14,18,19} Two studies also reported that RAGE^{-/-} mice challenged with LPS had the same degree of inflammatory cell influx as WT mice.^{13,18}

Plasma cytokine levels

Six studies reported the impact of RAGE inhibition on plasma cytokine levels during sepsis. For polymicrobial infection, Liliensiek et al. found that the plasma cytokine levels did not differ significantly between the RAGE^{-/-} group and the WT group.⁹ For G⁺ bacterial infection, van Zoelen et al.¹¹ found that interleukin (IL)-6 was reduced in the RAGE^{-/-} group, while Achouiti et al. found that tumor necrosis factor (TNF)- α and IL-6 were both reduced in the RAGE^{-/-} group.¹⁵ For G⁻ bacterial infection, van Zoelen et al.¹², Achouiti et al. and Noto et al. all found that the anti-inflammatory cytokine IL-10 was elevated in the RAGE^{-/-} group.^{18,19}

Pulmonary injury

Five studies reported the impact of RAGE inhibition on pulmonary injury during sepsis. For G^+ bacterial infection, both van Zoelen et al.¹¹ and Achouiti et al. found reduced pulmonary injury in the RAGE^{-/-} group compared with the WT group.¹⁶ For G^- bacterial infection, although Ramsgaard et al. showed that the RAGE^{-/-} group had reduced pulmonary injury, both van Zoelen et al.¹² and Achouiti et al. found no significant differences between the comparison groups.^{13,18}

Discussion

RAGE functions as a sensor of danger signals, triggering a certain degree of inflammatory reactions. This process can act as a double-edged sword during sepsis, on the one hand protecting the host against invading pathogens; however, destroying cells and tissues.²⁰ In this comprehensive systematic review and meta-analysis, we analyzed and described the effects of RAGE inhibition on the sepsis survival rate in animal models. The overall meta-analysis showed that RAGE inhibition was associated with a significantly higher survival rate than the control (HR 0.67, 95% CI 0.52–0.86, $P=0.001$). However, this therapeutic effect varied greatly during subgroup analysis of the type of infection. The effect was most pronounced in polymicrobial infection (HR 0.28, 95% CI 0.14–0.55, $P=0.0002$), followed by G^+ infection (HR 0.70, 95% CI 0.50–0.97, $P=0.03$) and G^- bacterial infection (HR 0.89, 95% CI 0.58–1.38, $P=0.60$).

One possible explanation for the intriguing observation that RAGE inhibition during different types of infections had differential effects on survival is that RAGE-mediated bacterial clearance might be pathogen dependent. To test this hypothesis, systematically reviewed the impact of RAGE inhibition on bacterial outgrowth and

dissemination. As expected, RAGE inhibition reduced bacterial outgrowth and dissemination to distant organs during G^+ bacterial infection, and to a lesser extent during G^- bacterial infection. Previous *in vitro* studies support these findings. Peritoneal macrophages harvested from RAGE^{-/-} mice have an increased capacity to kill *S. pneumoniae* (a G^+ bacterium), whereas RAGE^{-/-} neutrophils have a reduced ability to phagocytose *K. pneumoniae* (a G^- bacterium).^{11,18} Taken together, these data suggest that the impact of RAGE inhibition on survival rate and bacterial clearance is likely to be at least in part determined by the specific microorganism involved.

For polymicrobial infection, the detected survival benefit was not associated with reduced bacterial outgrowth and dissemination.¹² This may be partly explained by previous findings showing that the host defense against CLP depends on the extent of intestinal necrosis and formation of a local abscess.²¹ Consequently, the impact of RAGE inhibition on bacterial clearance might not be easily determined using this sepsis model.

Mortality from sepsis is thought to be a consequence of excessive inflammatory cell influx into the infection site, combined with an over-production of pro-inflammatory and anti-inflammatory cytokines in the blood. All these inflammatory alterations contribute to tissue damage, multiple organ dysfunction syndrome (MODS), and secondary opportunistic infections.²² Thus, we also conducted a systematic review of inflammatory cell influx, plasma cytokine levels and pulmonary injury between the RAGE inhibition and control groups. We found that RAGE inhibition was associated with reduced inflammatory cell influx, plasma cytokine levels and pulmonary injury during G^+ bacterial infection, and these parameters correlated with enhanced survival.

It is still unclear whether RAGE interact with ligands from pathogens and whether

the RAGE-induced effects in first-line defense mechanisms are pathogen dependent. If so, then these mechanisms might explain the opposite effects of RAGE inhibition on survival, bacterial clearance and inflammatory reactions observed with different methods of sepsis induction. However, such mechanisms remain speculative and require further investigation to confirm their existence.²³

Lutterloh et al. found that an anti-RAGE antibody protected mice from mortality in CLP induction of sepsis, and the survival benefit was comparable to that of a RAGE gene knockout. Furthermore, the anti-RAGE antibody enhanced survival even when administration started up to 24 h after CLP.¹⁰ Studies investigating the effects of sRAGE, which acts as a decoy receptor, in murine CLP-induced sepsis found that sRAGE administration improved the 7-day survival rate compared with controls.^{9,24} We did not include studies involving sRAGE in our analysis due to its interaction with receptors other than RAGE itself. However, these studies combined suggest that anti-RAGE antibodies and sRAGE might be attractive therapeutic agents for treating sepsis in clinical settings.

Some limitations of our systematic review and meta-analysis are worth noting. First, there is more bias in systematic reviews of animal models than in clinical trials. According to the CAMARADES checklist, the overall quality of the studies included in this analysis was not particularly good. Second, the number of studies that met our inclusion criteria was small, and the limited data available was insufficient for certain comparisons, such as subgroup analysis. Third, the literature was unclear as to which experimental approach was most appropriate for evaluating the effects of RAGE inhibition on sepsis in animal models. Various methods were used for inducing sepsis in these studies, and including all types of experimental sepsis together

in this analysis could overestimate or underestimate the role of RAGE inhibition. Fourth, we also found various RAGE inhibition methods, including RAGE gene knockout, or administration of anti-RAGE antibody or sRAGE. Because of its interactions with multiple receptors, sRAGE-related studies were excluded. However, this inevitably excluded some valuable information. Fifth, the different methods of collecting samples, time points, and outcome measurement criteria in the included studies would have contributed substantially to the high heterogeneity. Sixth, the authors did not report any information about the stage of sepsis and whether septic shock was present in the animals studied. The state of sepsis could be an important consideration when evaluating the therapeutic value of RAGE inhibition. Seventh, many of the studies were carried out by groups that were led by the same senior investigator, which might limit the generalizability of the results.

Conclusions

Based on the results of our analysis, RAGE inhibition enhances survival in animal models and may protect against sepsis. Therefore, RAGE may be a promising therapeutic target for treating sepsis clinically. However, the observation that RAGE inhibition is beneficial in sepsis that is induced by one method and ineffective in another suggests that RAGE-mediated pathogen defenses may rely on distinct mechanisms. Further investigations are needed to define the role of RAGE inhibition in different infectious conditions.

Compliance with Ethical Standards

Ethical approval

The authors did not directly carry out any research involving human participants or animals in this study.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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