Review Article

Immunomodulatory drugs in sepsis: a systematic review and meta-analysis

R. C. Robey,[1,2] **C. Logue,**[3] **C. A. Caird,**[3] **J. Hansel,**[4,5] **T. P. Hellyer,**[6] **J. Simpson,**[7] **P. Dark,**[8,9] **A. G. Mathioudakis**[5,10] and **T. Felton**[11,12]

1 Honorary Research Fellow, 4 NIHR Academic Clinical Fellow, 10 NIHR Clinical Lecturer, 11 Clinical Senior Lecturer, Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
2 NIHR Academic Clinical Fellow and Medical Registrar, 3 Senior House Officer, 5 Registrar, 12 Consultant, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, UK
6 Clinical Senior Lecturer and Honorary Consultant, 7 Professor, Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK
8 Chair and Professor, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
9 Honorary Clinical Consultant, Critical Care Unit, Northern Care Alliance NHS Foundation Trust, Salford Care Organisation, Salford, UK

Summary

Dysregulation of the host immune response has a central role in the pathophysiology of sepsis. There has been much interest in immunomodulatory drugs as potential therapeutic adjuncts in sepsis. We conducted a systematic review and meta-analysis of randomised controlled trials evaluating the safety and clinical effectiveness of immunomodulatory drugs as adjuncts to standard care in the treatment of adults with sepsis. Our primary outcomes were serious adverse events and all-cause mortality. Fifty-six unique, eligible randomised controlled trials were identified, assessing a range of interventions including cytokine inhibitors; anti-inflammatories; immune cell stimulators; platelet pathway inhibitors; and complement inhibitors. At 1-month follow-up, the use of cytokine inhibitors was associated with a decreased risk of serious adverse events, based on 11 studies involving 7138 patients (RR (95%CI) 0.95 (0.90–1.00), I^2 = 0%). The only immunomodulatory drugs associated with an increased risk of serious adverse events were toll-like receptor 4 antagonists (RR (95%CI) 1.18 (1.04–1.34), I^2 = 0% (two trials, 567 patients)). Based on 18 randomised controlled trials, involving 11,075 patients, cytokine inhibitors reduced 1-month mortality (RR (95%CI) 0.88 (0.78–0.98), I^2 = 57%). Mortality reduction was also shown in the subgroup of 13 randomised controlled trials that evaluated anti-tumour necrosis factor α interventions (RR (95%CI) 0.93 (0.87–0.99), I^2 = 0%). Anti-inflammatory drugs had the largest apparent effect on mortality at 2 months at any dose (two trials, 228 patients, RR (95%CI) 0.64 (0.51–0.80), I^2 = 0%) and at 3 months at any dose (three trials involving 277 patients, RR (95%CI) 0.67 (0.55–0.81), I^2 = 0%). These data indicate that, except for toll-like receptor 4 antagonists, there is no evidence of safety concerns for the use of immunomodulatory drugs in sepsis, and they may show some short-term mortality benefit for selected drugs.

Correspondence to: R. C. Robey
Email: rebecca.robey@doctors.org.uk
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Twitter/X: @VirtueOfNothing; @hellyerthomas; @MathioudakisAG; @timwfelton

Introduction

Sepsis is a heterogeneous syndrome of life-threatening organ dysfunction resulting from infection [1]. It is estimated to have a global burden of 30 million cases and is associated with 6 million deaths annually [2]. In 2017, the World Health Organization adopted a resolution to reduce the burden of sepsis through improved prevention, diagnosis and management [2].

Despite improved understanding of the pathophysiology of sepsis, the mainstay of treatment remains timely appropriate antimicrobial therapy, infection source control, resuscitation and organ support [3]. The central role of the dysregulated host immune response in sepsis means there has been much interest in drugs that target various components of this as potential therapeutic adjuncts. The original understanding and consensus definition of sepsis was as a ``*systemic inflammatory response syndrome*´´ arising in response to infection [4]. Consequently, early trials focused on drugs that blocked components of the inflammatory cascade such as tumour necrosis factor α (TNFα) antagonists [5] and interleukin (IL)-1 receptor antagonists [6]. However, it is now clear that the deranged and deregulated host response that is the hallmark of sepsis is more complex, involving sustained excessive inflammation, immunosuppression and a failure to return to normal homeostasis, with both pro- and anti-inflammatory responses contributing to the pathological state [7–9]. Furthermore, the release of pro- and anti-inflammatory cytokines can lead to down-regulation of the adaptive immune system by negative feedback, with down-regulation of cell-surface molecules such as human leukocyte antigen DR (HLA-DR), increased expression of inhibitory immune checkpoint molecules such as programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PD-L1), increased immune cell apoptosis and T-cell exhaustion [9]. Subsequently, immune stimulators such as PD-1/PD-L1 inhibitors have also been investigated [10].

Unfortunately, there remains a remarkable contrast between the advances in understanding sepsis pathophysiology and the lack of progress in the development of therapies targeted at modifying the dysregulated host response in sepsis [7, 11]. Despite numerous randomised controlled trials (RCTs) of immunomodulatory drugs in sepsis, none have resulted in new treatments [11]. However, the apparent failure of drugs in clinical trials may not be due to ineffectiveness per se, but rather to our current lack of ability to identify the appropriate patient groups, or indeed the appropriate time of delivery, that may confer benefit from each specific therapy [3, 8, 11, 12]. As we move closer to an era of precision and personalised medicine and our understanding of the dynamics of hyper-inflammation and immunosuppression in sepsis grows, there may be renewed interest in some of these therapies, especially if we are able to determine whom they may benefit and when [3, 8, 11, 12].

Furthermore, the response to IL-6 inhibition in patients with COVID-19 pneumonitis shows the potential for immunomodulatory drugs in a single pathogen infectious disease process [13, 14]. This, together with growing concerns regarding the lack of new antimicrobials and the emergence of multidrug-resistant bacteria, should refocus efforts on host-directed therapies that in principle should remain effective against multidrug-resistant micro-organisms [15]. We therefore conducted a meta-analysis of RCTs of targeted immunomodulatory drugs in sepsis with the aim of addressing whether these therapies are safe to use in sepsis and if there is any evidence of clinical effectiveness, specifically with respect to mortality benefits.

Methods

We based this study on a protocol prospectively registered with an international prospective register of systematic reviews. We conducted and reported the findings following the methodology recommended by the Cochrane Collaboration [16] and the PRISMA statement [17], respectively.

The Cochrane Library (CENTRAL), PubMed/Medline and ClinicalTrials.gov were searched from inception until 20 March 2023 for RCTs completed and reported in peer-reviewed manuscripts in the English language. A comprehensive search strategy that included both free search terms and controlled vocabulary was used to look for relevant RCTs (online Supporting Information Appendix S1). After de-duplication, all studies yielded by the searches were screened by two co-authors independently at a title/abstract level, followed by a full-text assessment of all potentially eligible studies. The references of all included studies were also screened. Relevant information regarding baseline characteristics, interventions and outcomes were extracted in a structured Excel form (Microsoft Corporation, Redmond, WA, USA) and the risk of bias was assessed using the Risk of Bias 2 tool [18] by one investigator and cross-checked by a second. Disagreements were resolved by discussion or adjudication by a third investigator when necessary.

Eligible studies comprised placebo-controlled RCTs evaluating the safety and efficacy of immunomodulatory drugs as adjuncts to standard care for adult patients with sepsis or septic shock. Following a pragmatic approach, we accepted a diagnosis of sepsis based on national or

international guidelines, commonly used severity scores or clinical judgement. Patients receiving either ward-based or critical care were eligible. Studies involving neutropenic patients were excluded. The list of potential interventions included any commercially available or experimental treatments that had a direct, targeted effect on known immunological pathways. We did not study passive immunotherapies (e.g. steroids), immunoglobulins, anti-inflammatories (e.g. ibuprofen) or anti-endotoxins (e.g. E5 or anti-LPS monoclonal antibodies). In addition, we did not study recombinant activated human protein C, drotrecogin alfa (a primary anticoagulant) the use of which in sepsis has already been subject to extensive review and meta-analysis elsewhere [19]. The list of immunomodulatory drugs was informed by Drugbank (accessed 08/05/2021), an online database containing information on drugs and drug targets [20], as well as PubMed/Medline searches. Table 1 shows the list of included immunomodulatory drugs. We included only the primary analysis of trials, and not post hoc analyses.

The primary outcomes assessed were the incidence of serious adverse events (SAEs) and all-cause mortality. The secondary outcome measure was the incidence of adverse events.

Our statistical analysis anticipated the potential for significant clinical and methodological heterogeneity and therefore we planned to conduct random effect meta-analyses and used the I^2 test to explore heterogeneity. We reported only dichotomous data as relative risks (RR) with 95%CIs. We corrected for zero event counts by adding one event in each treatment group, in cases where the study population exceeded 20 patients per group. Smaller studies with zero events in any of the relevant treatment groups were excluded from the respective meta-analyses. Immunomodulatory drugs were grouped based on their mechanism of action into six broad categories and analysed together (Table 1). In anticipation of included trials testing various medicine doses, we planned to conduct two analyses evaluating the highest treatment dose and then any treatment dose assessed. We also planned to evaluate only the approved doses of licensed treatments but found that a large proportion of treatments were still experimental (not approved for use in any disease entity) and so we were unable to complete this analysis. In a sensitivity analysis we repeated all meta-analyses using fixed-effect models and, to address considerable heterogeneity (> 70%), we assessed patients by treatment setting (hospital vs. intensive care unit) and individual drugs separately. Visualisation of the funnel plots and assessment of Egger's regression and Begg's rank correlation were used to test for potential publication bias for meta-analyses involving at least 10

Table 1 Identified immunomodulatory drugs grouped by mechanism of action.

Mechanism of action	Interventions
Anti-inflammatory treatment	Anti-CD14 monoclonal antibody Bradykinin antagonist Group IIA secretory phospholipase A2 inhibitor Thymosin alpha (peptide fragment of prothymosin alpha), with or without ulinastatin (urinary trypsin inhibitor) Triggering receptor expressed on myeloid cells 1 (TREM-1) inhibitor
Complement inhibition	C1-esterase inhibitor C1-inhibitor Anti-C5a
Cytokine inhibition	Anti-tumour necrosis factor α Interleukin-1 receptor antagonist P55 tumour necrosis factor receptor (TNFR) fusion protein
Immune cell stimulation	Anti-programmed death ligand 1 (immune checkpoint inhibitor) Granulocyte colony-stimulating factor Granulocyte-macrophage colony-stimulating factor Interleukin-7
Platelet pathway inhibition	Platelet-activating factor acetylhydrolase Platelet-activating factor antagonist Platelet-activating factor receptor antagonist
Other	Toll-like receptor 4 antagonists Interleukin receptor 1 antagonist *OR* recombinant interferon-gamma*

*One study [38] used either interleukin receptor 1 antagonist OR recombinant interferon-gamma as an intervention depending on the patient's characteristics. Only pooled results were reported (no individual results for the different interventions) and so this intervention was classed as `other´ due to the different mechanisms of action of the two interventions.

studies (online Supporting Information Figure S1). Meta-analyses were conducted in R, version 3.6 or newer, using the packages ``meta'' and ``forestplot'' (R Studio, Vienna, Austria).

Results

Details of the study selection process are shown in Figure 1. After de-duplication, we assessed 3720 unique titles, from which we identified 56 eligible RCTs. The most frequently assessed intervention group was cytokine inhibitors (n = 19), followed by anti-inflammatories (n = 12); immune cell stimulators (n = 10); platelet pathway inhibitors (n = 8); complement inhibitors (n = 3); or other interventions (n = 4). Forty-one studies (73%) only recruited patients admitted to intensive care, the remainder included any patient hospitalised with sepsis (13 studies, 23%) or did not state the setting (two studies, 4%). A brief description of the included studies is shown in the online Supporting Information Table S1.

Overall risk of bias was considered low in 15 (27%) and high in nine (16%) of the included studies, with the remaining trials characterised as moderate risk of bias (some concerns) (online Supporting Information Table S2). Concerns for potential bias were most frequently due to: limited description of the randomisation process; deviations from the intended interventions; or missing outcome data.

Our primary outcome measure, the incidence of SAEs, was mostly evaluated at 1 month of follow-up, except for a small study assessing immune cell stimulators that also reported SAEs at 3 months [10]. At 1 month, the use of cytokine inhibitors at any dose showed a decreased rate of SAEs, based on 11 studies involving 7138 patients, RR (95%CI) 0.95 (0.90–1.00), I^2 = 0% (Fig. 2a). This remained unchanged when evaluating only the highest treatment dose used in each study (nine studies, 6018 patients, RR (95%CI) 0.95 (0.90–1.00), I^2 = 0%) (Fig. 2b). Of note, two of the RCTs evaluating cytokine inhibitors provided only pooled data for both doses investigated and so were excluded from the `high dose´ analysis [21, 22].

The category of drugs labelled `other´ at any dose was associated with an increase in SAEs at 1 month, RR (95%CI)

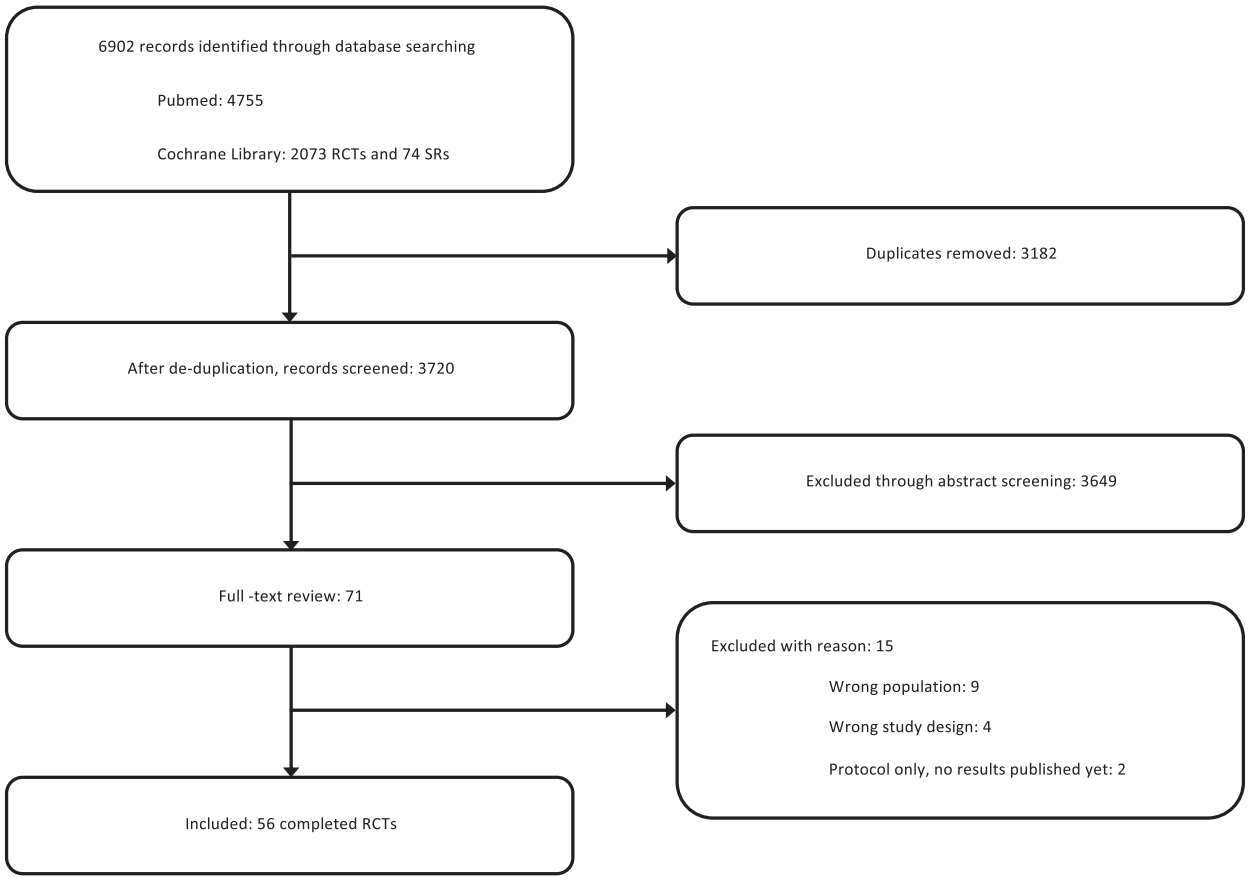


Figure 1 Study flow chart. RCTs, randomised controlled trials; SR, systematic reviews.

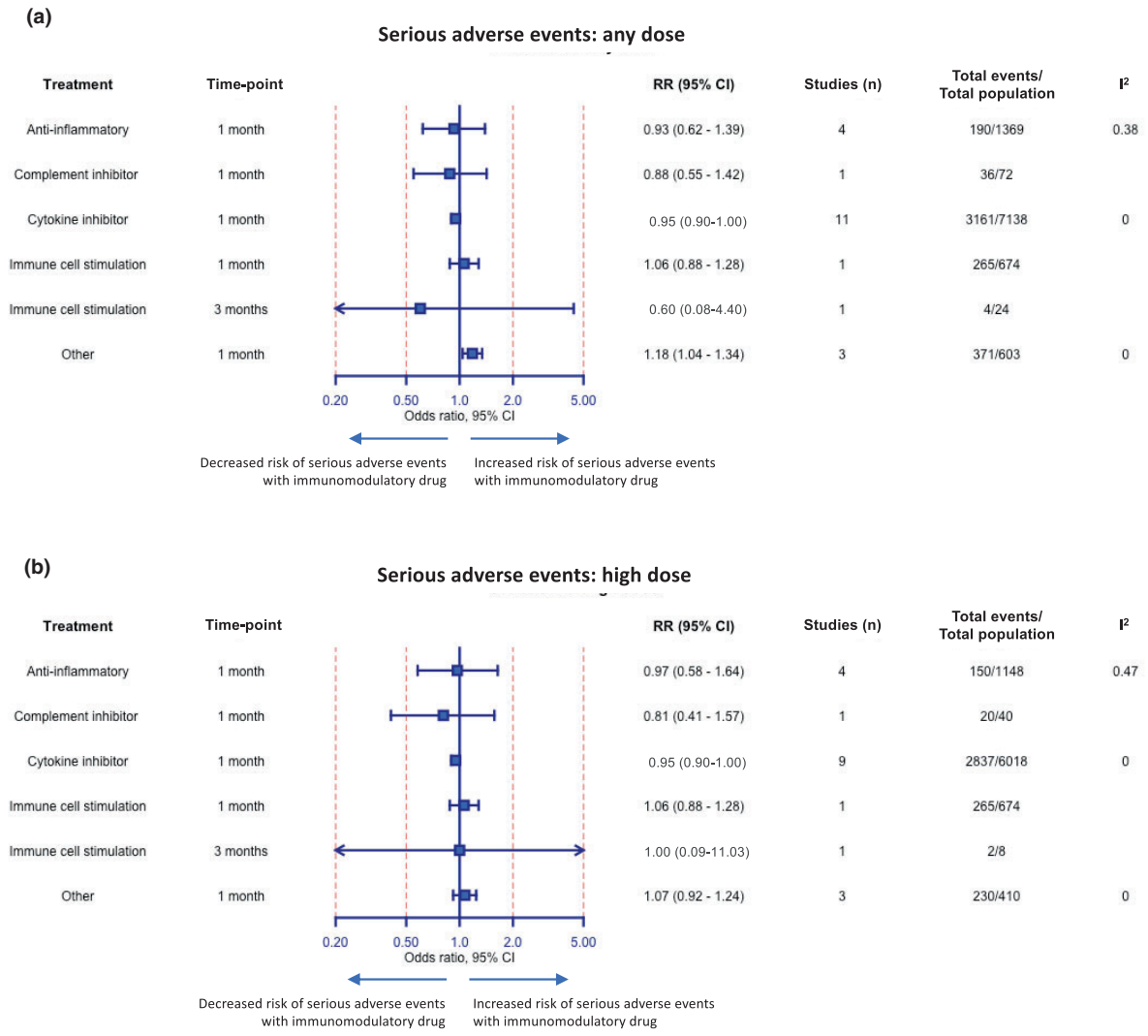


Figure 2 Pooled analysis of the frequency of serious adverse events in treatment groups compared with placebo as reported in randomised controlled trials of different categories of immunomodulatory drugs. (a) drugs used at any dose and (b) data for the highest dose of drug used for each trial.

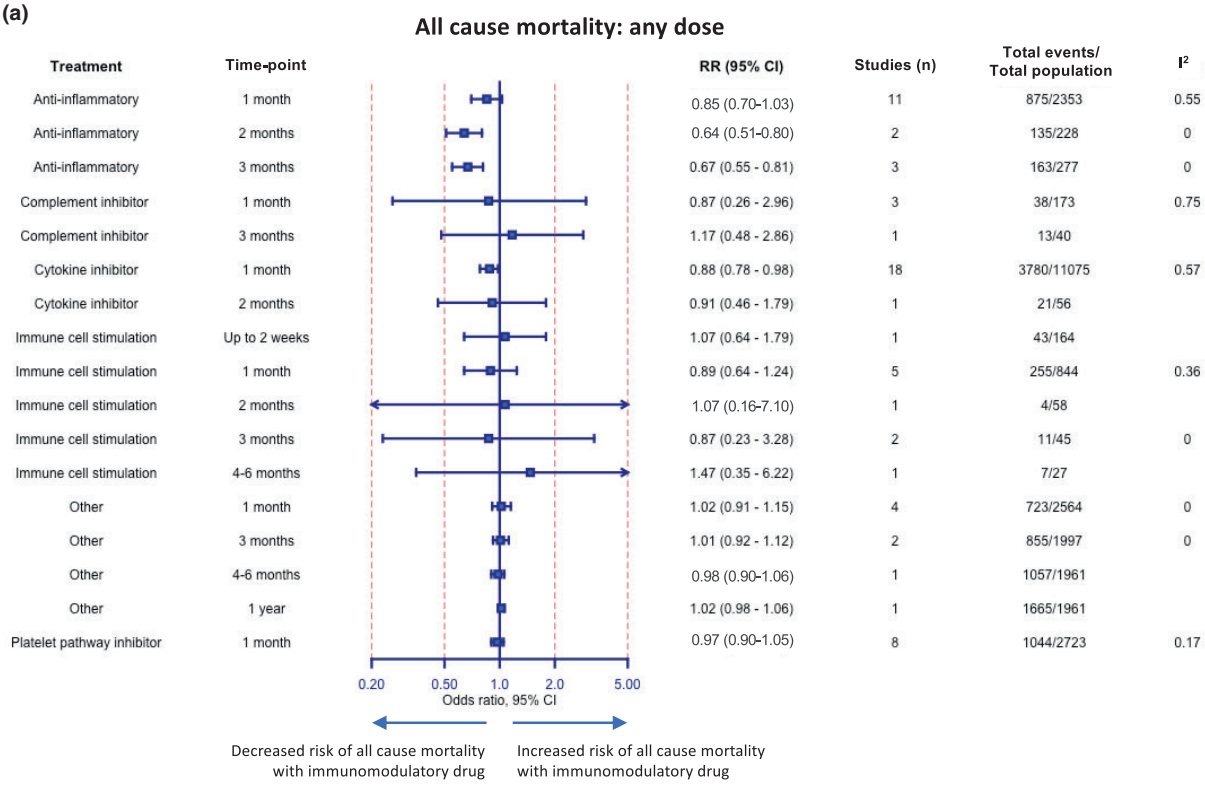
1.18 (1.04–1.34), I^2 = 0%; however, this effect was lost when analysing data for high dose only, RR (95%CI) 1.07 (0.92–1.24) (Figs. 2a and 2b). Within this category, the subgroup of toll-like receptor 4 antagonists was associated with an increased risk of SAEs at 1 month when any dose was analysed, based on two studies, 567 patients, RR (95%CI) 1.18 (1.04–1.34), I^2 = 0%. (online Supporting Information Appendix S2, p68). It was not clear from the data provided in the trial publications what type of SAEs were driving this. Furthermore, evidence for the increased RR based on 95% CIs was lost when only including the highest treatment dose, likely due to the limited overall sample size (two studies, 374 patients, RR (95%CI) 1.06 (0.91–1.24), I^2 = 0%). (online Supporting Information Appendix S2).

Anti-inflammatory drugs, complement inhibitors or immune cell stimulators did not impact the frequency of SAEs at any time-point (Figs. 2a and 2b).

When assessing the effect on mortality, all-cause mortality was mostly reported at 1 month (49 trials), but some trials reported this outcome at different time-points and analyses were grouped accordingly: up to 2 weeks (1 trial); 2 months (4 trials); 3 months (8 trials); 4–6 months (2 trials); and 1 year (1 trial).

Anti-inflammatory drugs and cytokine inhibitors were associated with reduced all-cause mortality, while there was no evidence of an association between any of the other treatment groups and this outcome. Based on 18 RCTs involving 11,075 patients, cytokine inhibitors at any dose

(a)



(b)

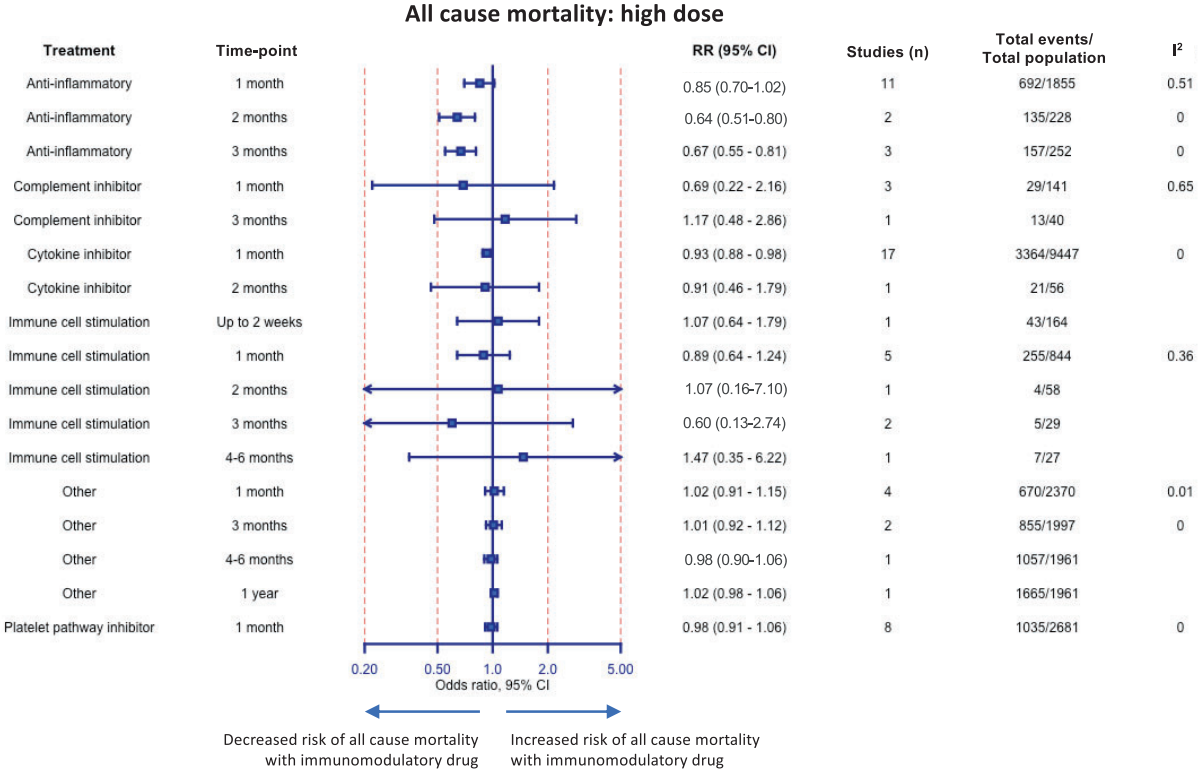


Figure 3 Pooled analysis of the risk of all-cause mortality in treatment groups compared with placebo as reported in randomised controlled trials of different categories of immunomodulatory drugs. (a) drugs used at any dose and (b) data for the highest dose of drug used for each trial.

reduced 1-month mortality by 12% (RR (95%CI) 0.88 (0.78–0.98), I^2 = 57%) (Fig. 3a). This effect was maintained when investigating the highest dose administered and the heterogeneity was resolved (17 RCTs, 9447 patients, RR (95%CI) 0.93 (0.88–0.98), I^2 = 0%) (Fig. 3b). Within this category, mortality reduction was also shown in the subgroup of anti-TNFα therapy. In 13 RCTs that evaluated anti-TNFα interventions in 7291 patients, there was a 7% reduction in mortality at 1 month (any dose, RR (95%CI) 0.93 (0.87–0.99), I^2 = 0%; high dose, RR (95%CI) 0.94 (0.88–1.00), I^2 = 0%). In contrast, the pooled data from three trials of interleukin inhibitors (any dose, RR (95%CI) 0.87 (0.76–1.01), I^2 = 18%; high dose, RR (95%CI) 0.87 (0.75–1.02), I^2 = 36%) and two trials evaluating p55TNFR fusion protein (any dose, RR (95%CI) 0.65 (0.31–1.37), I^2 = 95%; high dose, RR (95%CI) 0.92 (0.79–1.07), I^2 = 0%) did not reveal any mortality impact (online Supporting Information Appendix S2).

Anti-inflammatory drugs had the largest apparent effect on mortality with a 36% reduction at 2 months at any dose (two trials, 228 patients, RR (95%CI) 0.64 (0.51–0.80), I^2 = 0%) and a 33% reduction at 3 months at any dose (three trials, 277 patients, RR (95%CI) 0.67 (0.55–0.81), I^2 = 0%), with the effect maintained at high dose (Figs. 3a and 3b). Subgroup analysis revealed these effects were due to trials evaluating the use of a combination of ulinastatin and thymosin alpha (1 month any dose, RR (95%CI) 0.64 (0.52–0.78), I^2 = 0%); 2 months any dose, RR (95%CI) 0.64 (0.51–0.80), I^2 = 0%; and 3 months at any dose; RR (95%CI) 0.66 (0.54–0.80), I^2 = 0% (online Supporting Information Appendix S2).

Secondary outcome measures of adverse events were mostly evaluated at 1 month (23 trials), but some trials reported this outcome at different time-points, and analyses were grouped accordingly: up to 2 weeks (3 trials); 2 months (3 trials); and 3 months (3 trials).

Immune cell stimulators appeared to increase the risk of adverse events at 2 weeks of follow-up (any dose: RR (95%CI) 1.56 (1.07–2.27); high dose, RR (95%CI) 1.56 (1.07–2.27)) (Figs. 4a and 4b). However, the data from these were based on one RCT of 164 patients investigating the use of granulocyte colony-stimulating factor [23] (online Supporting Information Appendix S2). The adverse events that were increased in this study were deranged liver function tests (bilirubin > 101 μmol.l^{-1}) and decreased platelet count (< 51 × 10^9.l^{-1}).

None of the other evaluated treatments appeared to impact on the risk of adverse events at any time-point. Sensitivity and subgroup analyses revealed consistent results. No publication bias was identified.

Discussion

We have presented data from, to the best of our knowledge, one of the first meta-analysis of RCTs investigating the use of targeted immunomodulatory drugs as adjuncts for the treatment of sepsis in adults. There has, understandably, been concern that targeting immune pathways in sepsis may be harmful. Importantly, our analysis reveals that, based on current evidence, most immunomodulatory drugs appear safe for use in sepsis, with comparable rates of SAEs and adverse events compared with placebo in the majority of trials. Moreover, in a pooled analysis from 11 RCTs, the use of cytokine inhibitors reduced the risk of SAEs at 1 month after treatment. In contrast, the only subgroup of drugs associated with an increased risk of SAEs were toll-like receptor 4 antagonists, which, in pooled analysis from two RCTs, were associated with an 18% increase in SAEs. Adverse events were neither increased nor decreased in the pooled analysis for any of the categories of drugs at any time-point, with the exception of one trial of granulocyte colony-stimulating factor which showed a 56% increase in adverse events up to 2 weeks after treatment [23].

After nearly two decades of trials attempting to ameliorate sepsis by targeting aspects of its complex immunopathology, the absence of new licensed therapies may seem like an indication that these strategies have proven ineffective. However, our analysis found that across 18 RCTs of cytokine inhibitors, there was a 12% reduction in all-cause mortality 1 month after treatment. Subgroup analysis of this category of drugs revealed that anti-TNFα drugs were associated with a 7% reduction in mortality at this time-point. The use of ulinastatin and thymosin alpha (a subgroup of the anti-inflammatory category) had the biggest apparent effect on mortality with a 36% reduction at 2 months at any dose, although these data came from the pooled analysis of only two RCTs of 228 patients [24, 25] and

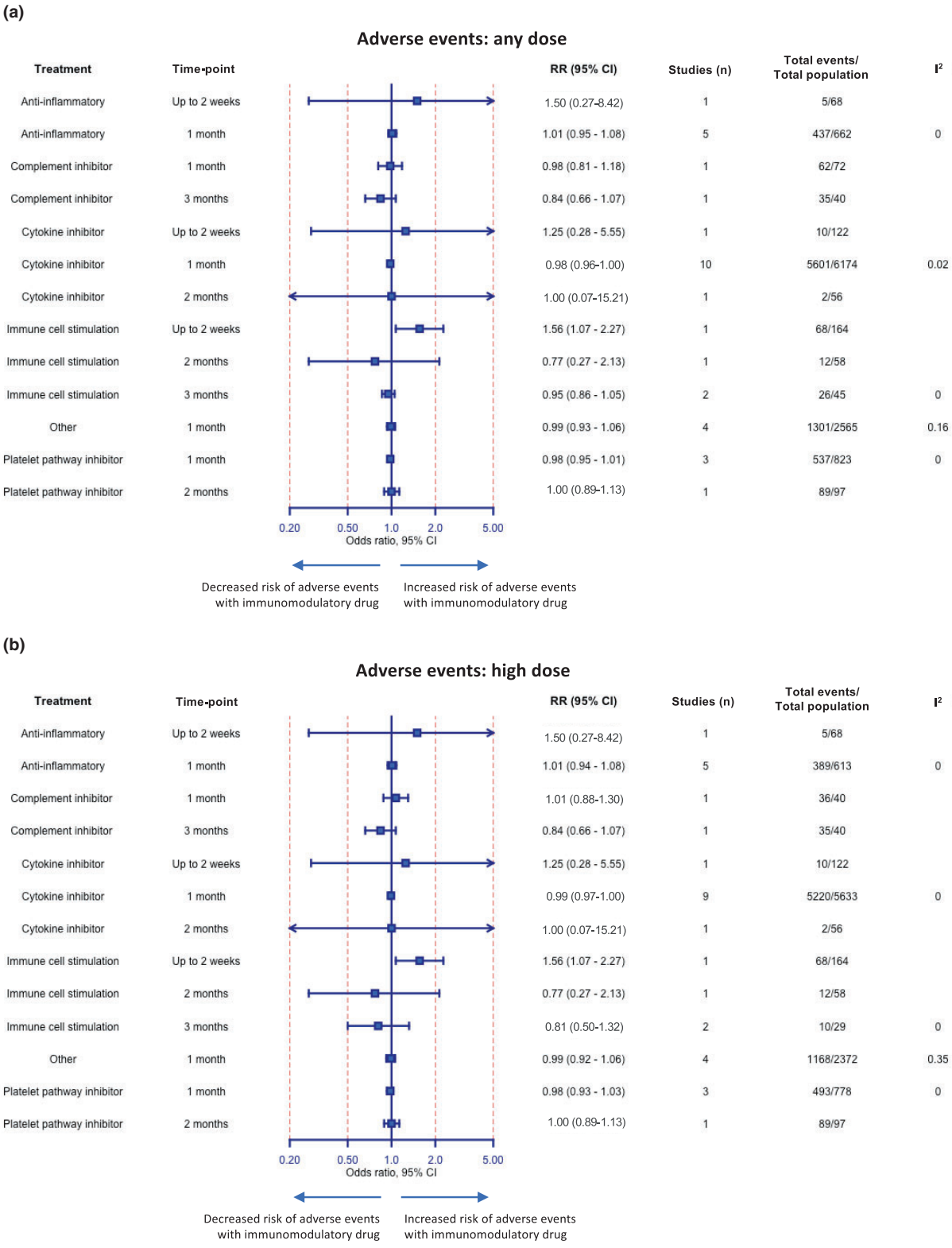


Figure 4 Pooled analysis of the frequency of adverse events in treatment groups compared with placebo as reported in randomised controlled trials of different categories of immunomodulatory drugs. (a) drugs used at any dose and (b) data for the highest dose of drug used for each trial.

both of these studies were assessed to be at high risk of bias. Moreover, we noted a very high degree of similarity in the data presented in the two studies.

A limitation of our study is the inherent issue that pre-licensed RCTs, despite being the principle initial means of establishing drug safety, are restricted in population size and duration and exclude high-risk populations; they therefore have limited statistical powers to detect rare SAEs in real-world patients [26]. Whilst meta-analysis can potentially overcome this in order to provide rigorous proof of the safety of an individual drug, achieving an optimal information size for that drug would be required [26]. This is beyond the scope of the present study, and indeed beyond that of the current available literature. Further safety monitoring is essential in future RCTs and beyond. A further limitation is that other efficacy outcomes of importance to patients such as duration of hospital or intensive care stay, duration of mechanical ventilation, disease severity scores, re-hospitalisation rates and quality of life were not addressed. These outcomes were rarely and inconsistently reported across the included trials.

This study focused on the impact of immunomodulatory drugs on mortality, adverse events and SAEs. These were broadly and homogeneously reported across the included trials and there was consensus among the authors that they represent the most crucial outcomes in sepsis. Unfortunately, heterogeneity in outcome reporting is a recognised limitation of meta-analyses and the use of a standardised, broad core outcome set of measures beyond survival is recommended for RCTs investigating sepsis in order to improve the quality of RCTs and enhance their comparability in meta-analysis [27–29]. However, the literature remains dominated by the pursuit of short-term mortality benefits [30] as supported by the results of this study. In response to the COVID-19 pandemic, an adjusted, pragmatic minimal core outcome set was proposed for use in COVID-19 [31]. We suggest it maybe timely to revisit the sepsis core outcome set similarly, to refine and adapt the recommendations, and importantly to re-promote its use.

As our understanding of the immunopathology of sepsis grows, it is becoming apparent that there may be distinct subsets of patients who are potential responders to therapy and this has been shown in post hoc trial analyses of specific subgroups of trial participants [32, 33]. Advances in genomics, proteomics, metabolomics and point-of-care technology, coupled with a better understanding of sepsis immunopathogenesis, mean that an era of personalised, precision immunotherapy is on the horizon [8]. As such, there is likely to be a renewed interest in this therapeutic strategy and new trial designs to try and identify the patient subgroups they may benefit.

Key to this will be the design of trials, supported by advances in observational and translational sepsis studies, that address and begin to unravel the heterogeneous nature of sepsis and how different therapies may be best matched to different patients. Precision prospective trials selectively recruiting patients according to biomarkers predicted to influence response is one possible approach. These could use simple serum biomarkers as predictors of response, selected due to biological plausibility, or identified by retrospective analyses of previous trials; for example, stratification of patients by baseline plasma IL-1ra concentrations as a predictor of response to recombinant IL-1ra therapy [33]. Alternatively, supported by advances in data science and machine learning, there is growing interest in the use of gene expression data to identify distinct sepsis phenotypes, defined by patterns of transcriptomic response to infection [34–36]. These phenotypes are associated with different clinical severity and outcomes and may have the potential to respond to different therapeutic approaches [35, 36].

The use of adaptive platform trials over conventional trial design may be ideally suited to future trials of immunomodulatory drugs in sepsis. This approach not only tests the effectiveness of multiple different therapeutic strategies but also explicitly considers the heterogeneity of the trial population with the goal of finding the best treatment for patient subgroups [35, 37]. The adaptive platform trial design fundamentally assumes treatment effects may be heterogeneous, and utilises response-adaptive randomisation, which uses accumulating outcome data to adjust randomisation probabilities to preferentially assign better-performing treatment regimens to future patients. Bayesian probabilities can also be used to determine if a treatment should be eliminated from a trial or from a subgroup of patients due to an accumulating lack of evidence of efficacy [37]. Moreover, the recent success of the RECOVERY and REMAP-CAP studies in using this approach to rapidly deliver treatments for COVID-19 [13, 14] shows that such a strategy has the potential to test, and hopefully deliver, new targeted treatments for sepsis within the next few years.

In conclusion, as our study shows a short-term mortality benefit for some drugs (even in unselected patient cohorts), we suggest that this provides support for future adequately powered trials within a new era of precision therapy trials, that should also consider longer-term patient-centred outcomes.

Acknowledgements

The protocol for this study was prospectively registered on PROSPERO (CRD42021254182). Data are available upon reasonable request to the corresponding author and may be used on condition of acknowledgement of its source from the authors of this paper (data includes data on serious adverse events, all-cause mortality and adverse event extracted from published reports of randomised controlled trials included in this study). Statistical code is not available. RR and JH are supported by a National Institute for Health Research Academic Clinical Fellowship. PD, AM and TF are supported by the National Institute for Health Research Manchester Biomedical Research Centre. PD is supported by a NIHR Senior Investigator award. No external funding or other competing interests declared.

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. Detailed search strategy.

Appendix S2. Individual forest plots.

Figure S1. Visualisation of the funnel plots.

Table S1. Summary of included studies

Table S2. Summary of risk of bias assessment for included studies.