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Adjunctive IgM-enriched immunoglobulin therapy with a personalised dose based on serum IgM-titres versus standard dose in the treatment of septic shock: a randomised controlled trial (IgM-fat trial)

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ABSTRACT

Introduction In patients with septic shock, low levels of circulating immunoglobulins are common and their kinetics appear to be related to clinical outcome. The pivotal role of immunoglobulins in the host immune response to infection suggests that additional therapy with polyclonal intravenous immunoglobulins may be a promising option in patients with septic shock. Immunoglobulin preparations enriched with the IgM component have largely been used in sepsis, mostly at standard dosages (250 mg/kg per day), regardless of clinical severity and without any dose adjustment based on immunoglobulin serum titres or other biomarkers. We hypothesised that a personalised dose of IgM enriched preparation based on patient IgM titres and aimed to achieve a specific threshold of IgM titre is more effective in decreasing mortality than a standard dose.

Methods and analysis The study is designed as a multicentre, interventional, randomised, single-blinded, prospective, investigator sponsored, two-armed study. Patients with septic shock and IgM titres <60 mg/dL will be randomly assigned to an IgM titre-based treatment or a standard treatment group in a ratio of 1:1. The study will involve 12 Italian intensive care units and 356 patients will be enrolled. Patients assigned to the IgM titre-based treatment will receive a personalised daily dose based on an IgM serum titre aimed at achieving serum titres above 100 mg/dL up to discontinuation of vasoactive drugs or day 7 after enrolment. Patients assigned to the IgM standard treatment group will receive IgM enriched preparation daily for three consecutive days at the standard dose of 250 mg/kg. The primary endpoint will be all-cause mortality at 28 days.

Ethics and dissemination The study protocol was approved by the ethics committees of the coordinating centre (Comitato Etico dell'Area Vasta Emilia Nord) and collaborating centres. The results of the trial will be published within 12 months from the end of the study and the steering committee has the right to present them at public symposia and conferences.

Trial registration details The trial protocol and information documents have received a favourable opinion from the Area Vasta Emilia Nord Ethical Committee on 12 September 2019. The trial protocol has been registered on EudraCT (2018-001613-33) on 18 April 2018 and on ClinicalTrials.gov (NCT04182737) on 2 December 2019.

Strengths and limitations of this study

- The IgM-fat trial is a large multicentre, interventional, randomised, single-blinded, prospective, investigator sponsored, two-armed study.
- The use of tailored dosages of IgM enriched preparation based on a biological marker, that is, IgM plasma levels, rather than standard dosages is consistent with the need for a more personalised approach in the appropriate use of this therapy in sepsis.
- The trial may provide useful information and substantial revision of the current indications for the use of intravenous polyclonal immunoglobulins in patients with septic shock.
- The maximum daily dose of 350 mg/kg per day allowed for safety reasons by regulatory agencies may delay the time for achieving the target of IgM plasma level and then, dampen the possible benefit, especially in patients with very low levels or a high turnover of immunoglobulins, and who are commonly patients with high mortality.
- The need for IgM plasma levels for study enrolment and for daily calculations of IgM enriched preparation in the treatment group may reduce the recruitment rate and the appropriate protocol application.

INTRODUCTION

Sepsis, one of the oldest, complex and elusive syndromes in medicine, is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection that can progress to septic shock characterised by profound abnormalities in tissue perfusion and cellular metabolism.[1–3] Despite recent advances, mortality rates in patients admitted to an intensive care unit (ICU) with septic shock remain remarkably high, ranging from 30% to 50% and those who survive are likely to have permanent organ damage, cognitive impairment and physical disability.[4–6] The high mortality related to sepsis is attributable to several factors including challenges in early patient identification, scarce compliance with recommended treatments, growing antimicrobial resistance and lack of true effective adjunctive therapies, particularly in patients with severe derangement of the immune system.[3 7–10] In patients with septic shock, low levels of circulating immunoglobulins are common and persistent low levels are related to poor clinical outcomes.[11–13] Immunoglobulins play a central role in the host inflammatory response through several different actions involving pathogens, mediators and immune cells.[4 14] These observations suggest that therapy with polyclonal intravenous immunoglobulins may be a promising option in patients with septic shock.[3 15 16] Although conclusive evidence from large numbers of randomised controlled trials are still lacking, several meta-analyses have reported a possible benefit of adjunctive therapy with polyclonal immunoglobulins in adults and children with sepsis and septic shock.[17 18] Furthermore, the above meta-analyses frequently observed a trend suggesting superior efficacy in reducing mortality in studies using IgM enriched preparations in comparison to those using pure IgG preparations. Since the first experiences reported more than 20 years ago, several retrospective and prospective clinical studies have highlighted significant advantages of using IgM enriched preparations in adults and neonates with sepsis and septic shock.[6 17–20] It must be noted that in previous clinical experiences, IgM enriched preparations were administered mostly at the standard dosages of 250 mg/kg per day for three consecutive days, regardless of the patient's severity and without any adjustment based on immunoglobulin plasma concentrations or other biomarkers. Recent understanding of the high heterogeneity in pathobiology of sepsis has led to recommendations for a more tailored patient approach by modulating therapies based on specific clinical and biological markers.[21 22] Therefore, the strategy of standard dosages of IgM enriched preparations needs to be reconsidered. We hypothesised that, in patients with septic shock, the personalisation of a daily IgM enriched preparation dosage on the basis of patient IgM titres to achieve a specific plasma level may provide more benefit than a standard dose.

METHODS AND ANALYSIS

Study objective

The objective is to verify whether adjunctive therapy with an IgM enriched preparation at a personalised dose based on patient serum IgM titres aimed at achieving specific plasma levels is more effective in reducing mortality in patients with septic shock compared with a standard dose therapy with IgM enriched preparation.

Mortality for any-cause will be assessed at 28 days.

Trial design and study setting

The study is designed as a multicentre, national, interventional, randomised, single-blinded, prospective, investigator sponsored, two-armed study. The study will involve 12 ICUs from Italian university and non-university hospitals well experienced in the management of patients with septic shock, the use of IgM enriched preparations as adjunctive therapy and investigator-initiated clinical studies. The timeline for assessment and procedures is outlined in table 1.

Population and recruitment

Patients with septic shock occurrence <24 hours at randomisation time and IgM titres <60 mg/dL (or <20% of the lower threshold value of the local laboratory) within 24 hours from shock occurrence will be enrolled. Septic shock is defined according to the Sepsis-3 definition.[2] Patients will be excluded if they have shock of uncertain diagnosis, hypersensitivity to the IgM enriched preparation in use or its excipients, intravenous immunoglobulin therapy for >6 hours before enrolment, selective absolute IgA deficiency with antibodies to IgA, pregnancy or breast feeding or a positive pregnancy test, clinical decision to withhold life-sustaining treatment or with the presence of other severe diseases impairing life expectancy (eg, patients who are not expected to survive 28 days given their pre-existing medical condition), neutrophil count of 40, participation in other clinical trials on adjunctive therapies for sepsis (during the past 3 months) and lack or withdrawal of informed consent. On the basis of a conservative estimation that the participating sites admit an average of three eligible patients per month per centre and assuming that 50% of eligible patients are enrolled, recruitment of 356 participants will be completed in around 24 months. An investigator meeting will be held before study commencement to discuss practical and operational issues. Every 2 to 4 months, recruitment status will be evaluated, and a newsletter will be disseminated, including any practical, clinical or scientific issues that may have arisen.

Randomisation and blinding

Patients who satisfy all inclusion criteria and have no exclusion criteria will be randomly assigned to an IgM titre-based treatment group (Group 1) or an IgM standard treatment group (Group 2) in a 1:1 ratio. Block randomisation will be used with variable block sizes (block size 4–6–8), stratified by centre. Central randomisation

Table 1 Timeline, data collection and outcomes of the study

Time points		Day 0	Daily from randomisation to ICU discharge: Day 1–7	Day 14	Day 21	Day 28	Day 90
Eligibility screen		X					
Informed consent		X or as soon as feasible					
Allocation		X					
Treatment:	Group 1	From day 0 to vasoactive drug discontinuation or day 7					
	Group 2	From day 0 to day 3					
Baseline characteristics[A]		X					
Physiological and process of care outcomes[B1]			X				
Physiological and process of care outcomes[B2]			X	X	X	X	
Primary outcome						X	
Secondary outcomes[C]			X				X
			X			X	

(A) Baseline characteristics: Demographic data (sex, date of birth), medical, medication and surgical history.
(B1) Physiological and process of care outcomes: Vital signs: mean arterial pressure, heart rate, respiratory rate, diuresis and systemic body temperature and fluid balance will be recorded daily from inclusion until ICU discharge (censored day 28), new blood, respiratory and urinary tract infections will be recorded from randomisation to day 28, viral reactivation measured by CMV DNA titres will be recorded from randomisation to day 28, need for renal replacement therapy: from randomisation to 28 days, IgM titres recovery/stabilisation: measured at day 28.
(B2) Physiological and process of care outcomes: Routine laboratory test parameters for organ function assessment: haemoglobin, platelet count, white blood cell count, troponin, coagulative parameters (INR, PT, aPTT), parameters for liver (AST, ALT, bilirubin) and renal function (creatinine) will be recorded daily from inclusion to day 7 and then at day 14, 21, 28, blood cell count, C-reactive protein and procalcitonin will be recorded daily from inclusion to day 7 and then at day 14, 21 and 28, ventilation mode (spontaneous breathing or mechanical ventilation), inspired oxygen fraction and arterial blood gas analysis parameters will be recorded daily from inclusion today 7 and then at day 14, 21 and 28.
(C) Secondary outcomes: 90-day survival; measured at day 90, occurrence of new organ dysfunction and grade of dysfunction: measured with SOFA score daily from randomisation to day 28 or ICU discharge, ICU free hours at 28 days; measured at day 28, hospital free days at 28 days; measured at day 28, ventilation free days at day 28; measured at day 28, vasopressor free days during the ICU stay; measured at day 28, antibiotic free days at day 28; measured at day 28, ICU acquired weakness; measured at 7, 28 and 90 days.
aPTT, activated partial thromboplastin time; AST, aspartate transaminase; CMV, cytomegalovirus; ICU, intensive care unit; INR, international ratio; PT, prothrombin time.

will be performed using a secure, web-based, randomisation system. The allocation sequence will be generated by the study statistician using computer generated random numbers. The attending physician, according to the protocol and the randomisation, will note the inclusion of the patient in the study. The study is conceived as single blinded and then, only the patients will not be aware of the group allocation.

Interventions

In Group 1 (IgM titre-based treatment), the treatment with IgM enriched preparation will be initiated as soon as possible after randomisation (maximum allowed starting time: 12 hours after randomisation). The calculation of the dose is based on IgM single compartment distribution. The first dose of IgM enriched preparation will be calculated based on IgM serum concentration obtained within 24 hours after shock appearance to achieve serum titres above 100 mg/100 mL. In subsequent days, the daily IgM enriched preparation dose will be calculated individually on the basis of morning IgM serum titre assessment, with the purpose of maintaining IgM serum titres above 100 mg/100 mL, up to discontinuation of vasoactive drugs or day 7 after enrolment. If the serum titre is above 100 mg/100 mL, the daily dose of IgM preparation will be zero, up to the daily serum titre decrease below 100 mg/100 mL. In this case, the patient will remain in the study despite not receiving the daily dose of IgM preparation. If, for whatever reason, IgM serum titres are not available, the daily dose will be calculated using the last IgM result obtained within 48 hours. Daily, the calculated dose will be administered for 24 hours in continuous infusion with a maximum infusion rate of 0.4 mL/kg per hour (20 mg/kg per hour) until reaching the calculated daily dose. The maximum IgM enriched preparation dose allowed throughout the study is 350 mg/kg per day, as reported from previous experiences.[20] In Group 2 (IgM standard treatment), the IgM treatment will be initiated as soon as possible after randomisation (maximum allowed starting time: 12 hours after randomisation). The dose of IgM preparation will be 250 mg/kg for 3 days and will be administered for 24 hours in continuous infusion with a maximum infusion rate of 0.4 mL/kg (20 mg/kg per hour) until reaching 250 mg/kg. The treatment given to patients of both groups will be the commercially available IgM enriched immunoglobulin preparation (Pentaglobin - TM, Biotest, Germany). The IgM enriched preparation contains high titres of antibodies against lipopolysaccharides and outer membrane proteins of many

Gram-negative bacteria and 1 mL solution contains 50 mg of human plasma protein of which at least 95% are immunoglobulins: 6 mg of IgM, 6 mg of IgA and 38 mg of IgG. In both groups, before enrolment, the administration of intravenous immunoglobulin preparations at standard dosages for a maximum of 6 hours will be allowed. The patients will be treated according to the principles of the Good Clinical Practice, Survival Sepsis Guidelines, 2016 and clinical judgement of the attending physician. No other pharmacological therapy or treatment will be influenced by the study protocol. There are no restrictions to concomitant treatments provided to patients in this study. All relevant concomitant medications and treatments taken or administered in the 24 hours before screening and during the study period will be recorded. Patients may be prematurely discontinued from study protocol at the discretion of the investigator if any untoward effects occur, including adverse events or clinically significant laboratory abnormalities that, in the opinion of the investigator, warrant the subject's permanent discontinuation from the study protocol.

Safety and monitoring

Previous studies did not identify specific risks correlated to intravenous immunoglobulin preparations enriched with IgM.[20 23 24] However, all included patients will be intensively monitored following the standard procedures of intensive care medicine and any suspected protocol related adverse event will be reported to the steering committee, the data safety and monitoring board, other participating centres and competent authorities. Beyond suspected protocol related adverse events, the data safety and monitoring board will have access to all trial results and make appropriate considerations about the appropriateness of the sample size, the efficiency and quality of the data collection system, and has the right to stop the trial for safety reasons or futility.

Outcome measurements

The primary endpoint of the study is the all-cause mortality at day 28 after enrolment. Secondary endpoints include all-cause mortality at ICU discharge, hospital discharge and at day 90, occurrence of new organ dysfunction and grade of dysfunction during ICU stay, ICU free hours (IFHs) at day 28, hospital free days (HFDs) at day 90, ventilation free days (VFDs) at day 28, vasopressors free days (VasoFDs) at day 28, antibiotic free days (AFDs) at day 28, ICU acquired weakness at 7, 28 and 90 days or hospital discharge and occurrence of protocol related adverse events at day 28 (safety endpoint). Organ dysfunction is defined as a Sequential Organ Failure Assessment (SOFA) score of ≥3 or a Multiple Organ Failure (MOF) score of ≥1 for the corresponding organ occurring after randomisation.[25 26] Grade of dysfunction is measured with the SOFA and MOF scores daily from randomisation to day 28 or ICU discharge. IFHs at day 28 are defined as the total number of hours between ICU discharge and day 28. If death occurs during the ICU stay before day 28, the IFHs' calculation will be zero. The ICU readmission before day 28 after randomisation will be considered. HFDs are defined as the total number of days between hospital discharge and day 90. If death occurs during the hospital stay before day 90, the HFDs' calculation will be zero. Hospital readmissions before day 90 after randomisation will be considered. VFDs are defined as the total number of days that a patient is alive and free of ventilation between randomisation and day 28 (censored at hospital discharge). Periods of assisted breathing lasting less than 24 hours for surgical procedures will not count against the VFDs' calculation. VasoFDs are defined as the total number of days that a patient is alive and free of vasopressors between randomisation and day 28 (censored at hospital discharge). AFDs are defined as the total number of days that the patient is alive and free of antibiotic drug administration between randomisation and day 28 (censored at hospital discharge). ICU acquired weakness will be assessed by the Medical Research Council (MRC) scale.

For measurements and outcomes whose collection in not censored at hospital discharge, data collection after hospital discharge will be performed by phone calls by the study investigators.

Power calculation for sample size analysis

On the basis of previous experience of patients with septic shock and low IgM titres, we assumed that the 28-day mortality rate will be 40% in the IgM standard treatment (Group 2) and 25% in the IgM titre-based treatment (Group 1). Considering a beta error of 20% and an alpha error of 2.9%, we calculated that a sample size (allocation ratio 1:1) including 178 patients in the IgM standard treatment Group 2 and 178 patients in the IgM titre-based treatment Group 1 will achieve 80% power to detect as statistically significant ($p<0.029$, Pocock probability level correction) the hypothesised difference between the two study arms (40% vs 25%). Alpha correction has been introduced according to an interim evaluation after inclusion and achievement of the primary outcome of 50% of patients into the study. Sample size has been quantified using the nQuery Advisor Procedure PTT0-1 for comparison of two proportions (χ^2 test). Based on the statistical hypothesis for sample size determination, a maximum of 356 patients will be included.

Statistical analysis

The intention-to-treat a population will be considered for primary analysis. A descriptive statistical analysis will be performed to describe every relevant variable. The Kolmogorov-Smirnov normality test will be performed in order to verify the variables' distribution. Categorical variables will be compared using Fisher's exact test. The primary outcome will be assessed by comparison of proportions of patients alive in both groups at day 28 by using Fisher's exact test. Comparing the treatment effect on the secondary outcomes will be assessed as follow: all-cause of mortality at ICU discharge, at hospital discharge and

at day 90 by Fisher's exact test; occurrence of new organ dysfunctions and grade of dysfunctions in the entire study period by Fisher's exact test and distribution free test such as median test, respectively; IFHs at 28-day, HFDs at day 90, VFDs at 28-day, VasoFDs at 28-day, AFDs at 28-day by distribution free test such as median; ICU acquired weakness assessed with the MRC scale by analysis of variance including terms for treatment, time and centre. Every test will be performed considering a two-sided p value <0.05 for statistical significance. In general, categorical data will be presented using counts and percentages, while continuous variables will be presented using the number of patients, mean, SD, median, minimum and maximum. A 95% CI will be calculated for the primary variable and for the relevant secondary variables. At the end of the study, a sensitivity analysis will be performed in which any withdrawn participant because of termination of the protocol at the discretion of the investigator is assigned to failed outcome.

Subgroup analysis

The primary and secondary outcomes will be evaluated in pre-defined subgroups: distribution of SAPS II (Simplified Acute Physiology Score II) and SOFA score (total and for single organ) at admission; surgical admissions compared with non-surgical admissions; type of pathogen causing septic shock, site and type of infection; distribution of IgM and IgG plasma concentrations at baseline and at day 3; biomarker (C-reactive protein and procalcitonin) distribution at baseline and at day 3; patients with end-stage liver disease compared with patients without and patients with malignancies compared with patients without.

Interim analysis

An interim analysis is planned after the randomisation of 178 patients (50% of sample size) with the double objective of monitoring safety and verifying the accuracy of the assumptions made for sample size estimation regarding the primary endpoint event rate in relation to the anticipated survival benefit. With the interim analysis, we will be able to evaluate whether there is a substantial superiority of one treatment. The results obtained will be evaluated by the DSMB (Data Safety Monitoring Board) and by the steering committee and, in case of significant differences in survival among the two groups, all patients will be switched to the most promising treatment.

DISCUSSION

In recent years, sepsis research has mostly focussed on inflammatory and immune responses to microorganisms and on the large heterogeneity in pathobiological phenotypes and clinical presentations.[27] In the face of this high variability, a more tailored approach of combining clinical signs and specific biomarkers able to characterise the host inflammatory immune response has been advocated for the appropriate use of adjunctive therapies. Regarding adjunctive therapy with polyclonal immunoglobulins, several studies have revealed that immunoglobulin titres are commonly low at the onset of sepsis and that during the sepsis course their changes are largely unpredictable.[11 12] In addition, persistent low levels of immunoglobulins are closely related to increased mortality. These premises generated the hypothesis that, in patients with septic shock, early adjunctive therapy with polyclonal immunoglobulin may be more beneficial in patients with low immunoglobulin titres and that daily dosages should be titrated to achieve adequate plasmatic concentrations. In other words, higher dosages may be required for restoring appropriate immunoglobulin concentration and functioning in patients with pronounced immunoglobulin deficits, while, on the other side, therapy with polyclonal immunoglobulin could not provide any advantage in patients with high plasmatic titres of immunoglobulin. With the aim of identifying a population at risk for high mortality, we decided to enrol only patients with septic shock and a documented IgM deficit defined as a plasmatic titre below 60 mg/dL. This threshold, as well as the IgM titre threshold of 100 mg/dL for calculating the daily dosages of IgM enriched preparation, have been defined on the basis of previously published experiences and of internal unpublished data from the Modena University Hospital including more than 250 patients treated with IgM enriched preparations.[11 12 28] The maximum daily dose originally proposed was 500 mg/kg per day but it was subsequently lowered to 350 mg/kg per day for safety reasons, as indicated by the ethical committee of the coordination centre and the Italian Medicine Agency. This may lead to a lengthening of the time necessary to achieve adequate IgM plasmatic concentrations with a potential dampening benefit, especially in patients with very low levels or a high turnover of immunoglobulins and who are commonly patients with high mortality. Additional studies will be needed to clarify whether higher dosages can be more effective and safely administered. Beyond the maximal dosages, other possible limitations of the study are the single-blinded design and the feasibility of the daily IgM plasma assessment and dose calculation in settings with low expertise in therapy with polyclonal immunoglobulin. To our knowledge, this is the first and only study using a specific immunoglobulin titre at shock onset as an inclusion criterion and with tailored dosages of IgM enriched preparation based on daily IgM titres. The confirmation of the superior efficacy of personalised dosages of IgM enriched preparation compared with standard dosages in reducing the mortality rate in patients with septic shock will lead to a substantial revision of the current clinical practice in the use of this adjunctive therapy. Trial Status Protocol V.3.0 of 22 December 2018 was approved by the Ethical Committee (EC) on 12 September 2019. Recruitment will begin in January 2020 approximately and will be completed in approximately 24 months.

ETHICS AND DISSEMINATION

Ethics

The entire study protocol, including informative material for the patients and modules for informed consent, has been approved by the local ethics committee of the coordinating centre (Comitato Etico dell'Area Vasta Emilia Nord), by the Italian Medicine Agency and by the ethics committees of the collaborating centres (Comitato Etico Regionale delle Marche, Comitato Etico Catania 1, Comitato Etico Campania Sud, Comitato Etico Cardarelli-Santobono, Comitato Etico Università degli Studi della Campania 'Luigi Vanvitelli' – A.O.U. 'Luigi Vanvitelli', A.O.R.N. 'Ospedali dei Colli'). The recruitment in each centre will not start before obtaining a favourable opinion from the EC, the Competent Authority Authorisation and any other authorisation required by local regulation. Every intention to modify any element of the original protocol after the first approval will be promptly notified to the ethics committee and will be applied only after its written authorisation.

Informed consent

Before inclusion in the study, conscious patients must be informed of the purpose, risks and benefits and of the clinical procedures required by the protocol. In addition, patients will be informed of their right to withdraw from the study at any time without explanation and without losing the right to future medical care. If the patient is unable to comprehend or to give their consent, the following consent options are acceptable: (1) a priori consent by a legal representative; (2) delayed consent from a legal representative; (3) delayed consent from the patient; (4) waiver of consent; and (5) consent provided by an ethics committee or other legal authority. All participants who recover sufficiently will be given the opportunity to provide informed consent for ongoing study participation and for the use of data collected for the study.

Dissemination

The Circ. Min. Health N° 6 of 09 February 2002 obliges each researcher who obtains any results of interest to public health, to publish the results within 12 months from the end of the study. The study coordinator is the official data owner. The steering committee has the right to present methods and results of the study at public symposia and conferences. The principal publications from the trial will be in the name of the investigators with full credit assigned to all collaborating investigators and institutions.

Patient and public involvement

No public and patient involvement.

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Competing interests GB and MG have received honoraria and lecture fees from Biotest Germany and Biotest Italy. The other authors declare that they have no competing interests in this section.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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