Examination of Setarud (IMOD™) in the management of patients with severe sepsis

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ABSTRACT

Background and the purpose of the study: Analysis of current immunomodulating strategies indicates that monovalent approaches are unlikely to restore immunostasis or achieve complete therapy of sepsis. Setarud (IMOD) as a mixture of urtica, carotenoids, urea, and selenium has been recently patented for its potential in reduction of Tumor Necrosis Factor alpha (TNF-α) and Interferon-γ and Interleukin-2 levels. The aim of this study was to examine efficacy of IMOD in the management of patients with severe sepsis.

Methods: Twenty patients with severe sepsis and acute physiology and chronic health evaluation (APACHE) score of more than 20 were randomized to receive standard treatment of severe sepsis (control group) or standard treatment plus IMOD (IMOD group). The group treated with IMOD for 14 days was according to the pilot study and regarding the stability of patient's conditions in the ICU. Of course patients in both groups received standard treatment and all were monitored for 28 days. Blood samples were analyzed for interleukins (IL-1, IL-2, IL-6), plasminogen activator inhibitor (PAI-1), TNF-α, total thiol molecules (TTM), nitric oxide (NO), total antioxidant power (TAP), and lipid peroxidation (LPO). Daily APACHE, Sequential Organ Failure Assessment (SOFA), and Simplified Acute Physiology Score (SAPS) were calculated.

Results and major conclusion: Comparing with controls, IMOD was significantly effective in improving SAPS, SOFA, and APACHE scores, and reduction of mortality rate. Among tested inflammatory biomarkers, IMOD significantly improved TTM and TNF-α values.

It is concluded that IMOD might be added as a safe adjutant to standard treatment of severe sepsis.

Keywords: Severe sepsis, IMOD, Immunomodulation, Setarud, ICU

INTRODUCTION

Sepsis is among the most common reasons for admission to intensive care units throughout the world and it represents a major burden to health care system. Regarding the complexities of sepsis, all aspects of body inflammatory response should be targeted to achieve better management of patients (1,2).

Following the initial host and microbial interaction, inflammatory cytokines are released by activated macrophages and CD_4 cells within the first hour after infection. Proinflammatory mediators are counteracted by antiinflammatory molecules such as IL-4, IL-10, and IL1-ra because CD_4 T cells can switch from the production of inflammatory cytokines to production of antiinflammatory cytokines (3). Immunotherapy must be applied at an early time point during the development of immunodysfunction following trauma or acute onset of infection to ensure that all cellular components of immune system are protected. There is much earlier temporal relationship between inflammation and the onset of organ dysfunction. Mean biomarker levels during 72 hrs were significantly greater in hospital non-survivors. Therefore, inflammatory elements such as TNF-α and IL-1 should be therapeutically targeted and neutralized (4). In early severe sepsis and septic shock, within the first 3 hrs of hospital presentation, distinct biomarker patterns emerge in response to hemodynamic optimization strategies (5). A significant association exists between temporal biomarker patterns in the first 72 hrs, severity of tissue hypoxia, organ dysfunction, and the mortality (6).

Analysis of current immunomodulating strategies indicates that monovalent approaches in isolation are unlikely to restore immunostasis or attain status of complete therapy. It is likely that multiple immunomodulating strategies will be necessary to achieve clinical success owing to complex interplay

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Table 1. Demographic and baseline characteristic of patients.

	Control Group	IMOD Group
Age (year)	52.20±14.42	37.60±20.26
Male/Female	50%	37.60%
APACHE II	27.60±7.21	30.40±4.57
SAPS	53.60±4.34	45.00±7.48
SOFA	7.80±4.52	7.00±5.12

Data are mean±SD. APACHE: Acute Physiologic And Chronic Health Evaluation. SAPS: Simplified Acute Physiologic Score. SOFA: Sequential Organ Failure Assessment.

between pathways. Botanical extracts provides cytoprotective, antiinflammatory, and antimicrobial activities in addition to immunoregulatory activity (7). Setarud (IMOD) is a mixture of urtica, carotenoids, urea, and selenium that can regulate TNF-α, interferone-γ (IFN-γ) and IL-2. IMOD has been patented in Europe with code of WO/2007/087825 for its immunomodulator and anti-TNF-α capacities and improving CD_4 in HIV positive patients (8). The pre-clinical safety studies of IMOD in animals, and phases I trials have been successfully conducted showing optimistic results (9,10). As sepsis is an immune mediated disease and IMOD has immunomodulatory properties, in this study its effect in management of patients with severe sepsis was evaluated.

METHODS

Subjects

Patients with severe sepsis and APACHE (Acute Physiology And Chronic Health Evaluation) score of more than 20 who admitted to general ICU of Sina Hospital of Tehran University of Medical Sciences were enrolled in this study.

Exclusion criteria were any of the following: age less than 18 years old, pregnancy, lactating women, organ transplant history, and death probability within 24 hrs.

Treatment protocol

This study was a randomized open labeled clinical trial that was approved by TUMS review board and registered at Australian Newzeland Clinical Trial Organisation with code number of (ACTRN012607000376448). Twenty patients with severe sepsis and APACHE score of more than 20 were enrolled in this trial. Patients were randomized to receive one of the following treatments: standard treatment for severe sepsis (control group) and standard treatment plus IMOD (IMOD group) for duration of 14 days. The group treated for 14 day with IMOD was selected according to the results of pilot studies and regarding the stability of patient's conditions in the ICU. Of course patients in both group received standard treatment and all were monitored for 28 days. According to last international guidelines, two recommended severe sepsis bundles were implemented as follow:

Severe sepsis resuscitation bundle, which began immediately not later than 6 hrs after diagnose of severe sepsis. The bundle contained serum lactate measurement, blood cultures before antibiotic administration, improving time to broad spectrum antibiotics, control of hypotension by vasopressors to target central venous pressure, and central venous oxygen saturation. The second bundle called sepsis management bundle began not later than 24 hrs after diagnosis of severe sepsis. The protocol contained administration of low dose of steroids, adequate glycemic control, and prevention of excessive inspiratory plateau pressure.

Patients in IMOD group received 125 mg (4 ml) of IMOD in 100 ml of DW5% which was infused over 1 hour on the first day. All hemodynamic data were noted during the infusion in order to stop it in the case of any negative hemodynamic deterioration, dermal rash, urticaria and anaphylactic reaction. Then 8 ml of IMOD in 100 ml of DW5% was infused everyday up to 14 days. The time gap between the beginning of treatment with IMOD and the diagnosis of sepsis was also noted to evaluate possible impact of the onset time of IMOD on mortality.

Demographic data and clinical information were obtained at the beginning (Table 1). Daily acute physiology and chronic health evaluation (APACHE), sequential organ failure assessment (SOFA), and simplified acute physiology score (SAPS) were calculated (4,11). Higher scores indicate more severe illness and a higher number of therapeutic interventions.

Death from any causes during intensive care, the number of days in the ICU, the need for mechanical ventilatory assist, renal replacement therapy, inotropic or vasopressor support, blood infection, and transfusion requirements were recorded. Of course after a 14-day protocol, the standard treatment of sepsis was continued during patients stay in the ICU. Mortality during ICU stay and mortality during 28 days were also noted.

Sample collection and handling

All patients had central venous catheters and arterial line for blood sampling. For all patients there were seven scheduled time points for determination of IL-1, IL-2, IL-6, plasminogen activator inhibitor (PAI-1), TNF-α, total thiol molecules (TTM), nitric oxide (NO), total antioxidant power (TAP), and lipid peroxidation (LPO) by the standard methods as described previously (12). The first sample was taken on ICU admission and before initiation of treatment. Other samples were obtained on days of 1, 2, 3, 7, 10, and 14 after starting of therapy. Blood samples were collected into vacutainer tubes containing EDTA. The samples were then centrifuged at 3000×g for 15 minutes, and the plasma was separated and stored at -80°C until analysis.

Table 2. Source of infection and detected organisms of patients

Source of infection	Abdomen	Lung	Urinary tract	Central nervous system	
Number of cases	3	5	3	3	
Detected organism	*Acinetobacter*	*P. Aeroginosa*	*S. Aerus*	*Klebsiella*	*C. Albicans*
Number of cases	3	5	2	5	1

Statistical analyses

The statistical analysis was performed using StatsDirect 2.6.6 software. Results were expressed as mean±SE. Because of small sample size and probability of abnormal distribution of data, the nonparametric test for comparison of intra and inter groups was used. Variations within groups (in comparison to baseline) were evaluated by Wilcoxon W test. Differences between two protocols were assessed by Mann Whitney test. *P*-value less than 0.05 was considered statistically significant.

RESULTS

Twenty patients with severe sepsis and APACHE score of more than 20 were included in this study. Two patients in IMOD group were excluded, one patient had positive lab results for HIV and another one needed amputation because of thrombotic gangrene of lower limb but he refused undergoing amputation.

Demographic and baseline values for APACHE, SAPS, and SOFA are presented in table 1. The source of sepsis and results of biological cultures are shown in table 2. The changes in biomarker values and mortality and morbidity during the study are shown in figures 1-12. Comparing with controls, IMOD was significantly effective in improving SAPS, SOFA, and APACHE scores. Among tested inflammatory biomarkers, IMOD significantly improved TTM and TNF-α. The changes of remaining biomarkers including IL-1, IL-2, IL-6, TAP, LPO, NO, and PAI were not different between groups.

In IMOD group, the mortality rate was 40% during 28 days while it was 50% in controls ($P<0.05$).

DISCUSSION

Despite great advancement in understanding of the pathophysiology and development of novel therapeutic approaches, mortality of sepsis remains unacceptably high (13). As mentioned earlier, the key point of severe sepsis is immune dysfunction suggesting that therapies should overcome immune dysfunction to improve clinical outcome. Several studies evaluated the effect of different treatments on severe sepsis, but failed to improve survival of patients for many different explanations. For example the experimental agents have been ineffective or the dose of experimental agents have been inadequate (14) or the timing of intervention has not been suitable (15, 16). In addition, there has been polymorphism (17) or heterogeneity (18) in patients under study. The treatment of sepsis is currently limited to activated protein C and moderate doses of corticosteroids. Activated protein C is associated with increased risk of hemorrhage that limits its use in patients with high risk of bleeding. High cost of activated protein C is another limitation. Previous studies have shown that monovalent therapies by itself could not restore immunostasis in severe sepsis (19), so the need to drugs with polyvalent activity like botanical immunodrugs seems inevitable (7). Botanical immunodrugs such as Chinese remedy and green tea have been found that dose-dependently attenuate bacterial endotoxin-induced HMGBI release (20). IMOD is a new herbal-derived remedy which has been already tested for toxicity in animals and found safe (11).

Results of this study indicated that TNF-α as the main inflammatory mediator of severe sepsis was reduced by IMOD treatment in comparison to controls. One of the outcomes of reduction in TNF-α would be the decline in many deleterious effects including inflammation, apoptosis, and cytotoxicity. Interestingly, it was found a significant elevation in TTM by IMOD during the treatment (Figure 9). Glutathione is the major low molecular weight thiol in the mammalian and it constitutes the most important antioxidant defense, thus measurement of TTM, allowed to monitor glutathione action. Although, positive effects of IMOD was not found on all biomarkers of inflammation or toxic stress but APACHEE, SOFA, and SAPS as quantitative indices of clinical status were improved by IMOD and mortality rate at the day of 28 was reduced. Improvement of APACHEE, SOFA, and SAPS by IMOD confirms potential of IMOD in alleviation of severity of disease and dynamics.

Fortunately, IMOD showed no adverse effect on coagulation factors like platelet count, prothrombine time, partial thromboplastin time, fibrinogen, and D-dimer. Hemodynamic instability and anaphylactoid reactions were not observed during infusion that is very important in septic patients who are vulnerable to little hemodynamic changes. Two patients in IMOD group had immune mediated thrombocytopenia which improved after treatment. In one patient under treatment with IMOD, a significant improvement in PaO2/FiO2 ratio was observed. Dose of 125 mg

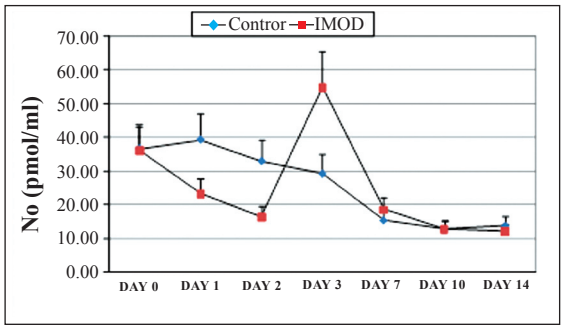

Figure 1. Changes in bood NO levels in different days of study. Data are mean±SE. Difference between two groups is not significant (P>0.05).

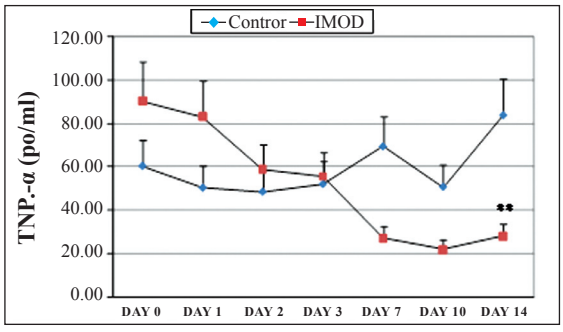

Figure 2. Changes in blood TNF-α level in different days of study. Data are mean±SE. **Difference between two groups is significant at P<0.01.

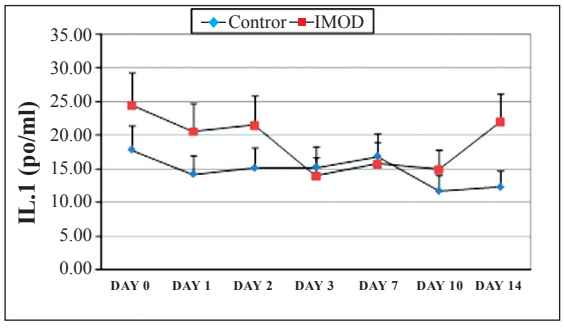

Figure 3. Changes in blood IL-1 levels in different days of study. Data are mean±SE. Difference between two groups is not significant (P>0.05).

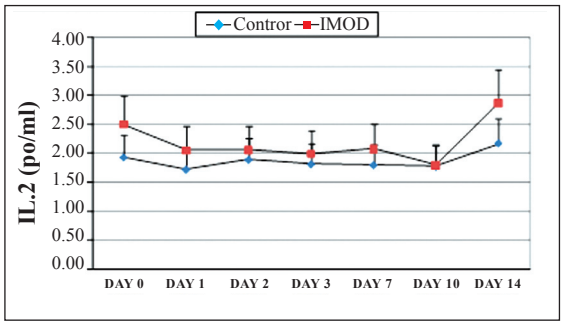

Figure 4. Changes in blood IL-2 levels in different days of study. Data are mean±SE. Difference between two groups is not significant (P>0.05).

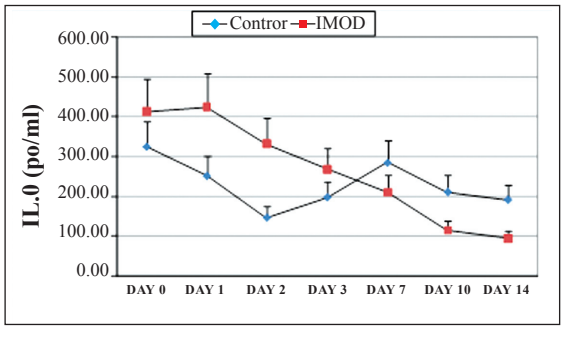

Figure 5. Changes in blood IL-6 levels in different days of study. Data are mean±SE. Difference between two groups is not significant (P>0.05).

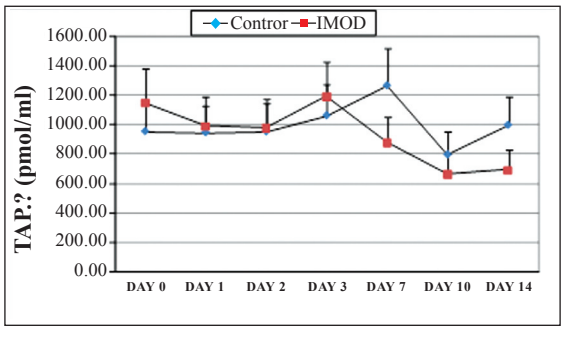

Figure 6. Changes in blood TAP in different days of study. Data are mean±SE. Difference between two groups is not significant (P>0.05).

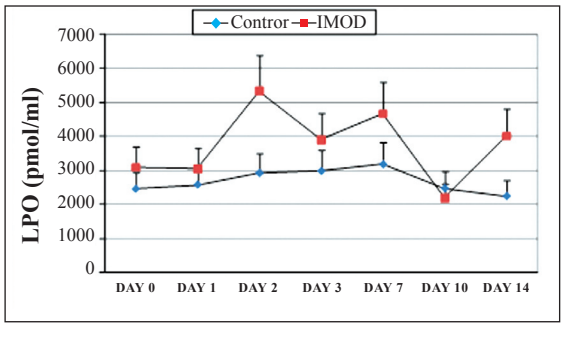

Figure 7. Changes in blood LPO in different days of study. Data are mean±SE. Difference between two groups is not significant (P>0.05).

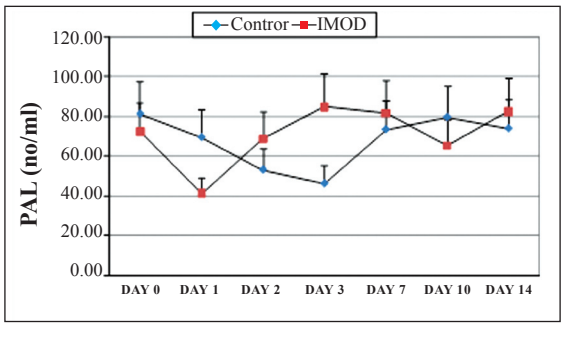

Figure 8. Changes in blood tPAI in different days of study. Data are mean±SE. Difference between two groups is not significant (P>0.05).

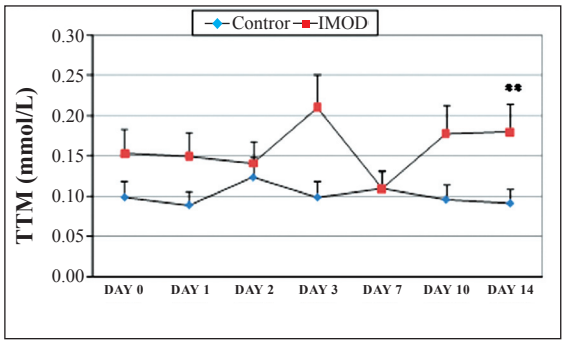

Figure 9. Changes in blood TTM in different days of study. Data are mean±SE. ** Difference between two groups is significant at P<0.01.

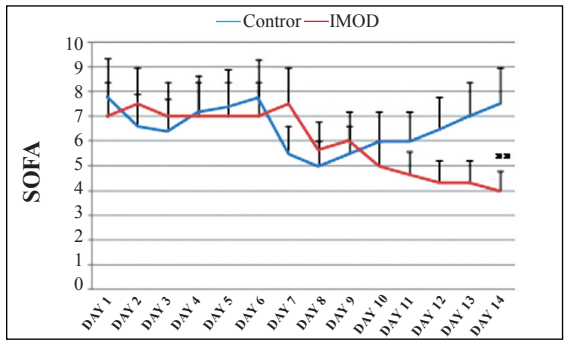

Figure 10. Changes of patients SOFA in different days of study. Data are mean±SE. ** Difference between two groups is significant at P<0.01.

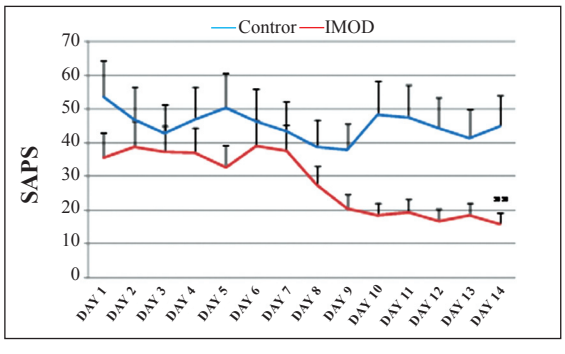

Figure 11. Changes of patients SAPS in different days of study. Data are mean±SE. ** Difference between two groups is significant at P<0.01.

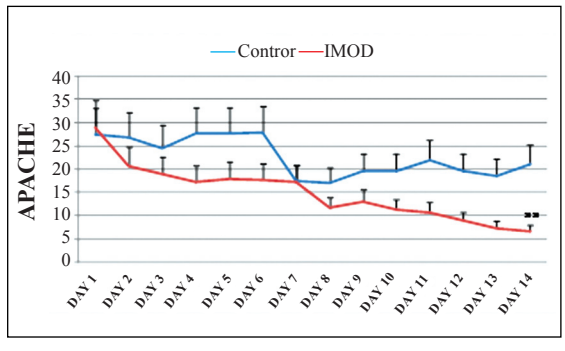

Figure 12. Changes of patients APACHE in different days of study. Data are mean±SE. ** Difference between two groups is significant at P<0.01.

for IMOD that was used in the present study is in the safe dose range and much less than toxic doses (10) and thus can be increased in future trials. One of limitations of the present study is small sample size but as a matter of fact it is difficult to have large sample size in ICU with critically ill patients because of heterogeneity of patients. In addition, a new study demonstrated that most of studies in ICU have the same limitations and endpoints other than mortality need to be considered when evaluating interventions in critically ill patients. It has been concluded that relatively few of the randomized controlled trials conducted in ICU show beneficial impact of the intervention on the survival (21).

Taking collectively, it is concluded that that IMOD may be added as a safe adjuvant to standard treatment of severe sepsis. This is the first study showing safety profile and possible antiinflammatory effect of IMOD in sepsis which might be extrapolated to acute respiratory syndrome and shock too. Further clinical trials with larger sample size and higher doses of IMOD are necessary to show exact antiinflammatory and immunomodulatory effects of IMOD in patients with septic shock.

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