Dear ladies and gentlemen, dear ADVOS users and interested parties,
we are pleased to present you another issue of our ADVOS Literature Service. We regularly select one or more papers from international journals which might be of interest to you in connection with our ADVOS procedure. This month we have selected the following:

REGISTRY ON EXTRACORPOREAL MULTIPLE ORGAN SUPPORT WITH THE ADVANCED ORGAN SUPPORT (ADVOS) SYSTEM: 2-YEAR INTERIM ANALYSIS.

Fuhrmann et al.

Key message

- Four hospitals in Germany participated in the EMOS registry and recruited 118 patients who received 429 ADVOS sessions accounting for more than 6,800 hours of therapy. This is the largest published cohort to date.
- The analysis confirmed the results of previous publications showing the ADVOS therapy as a feasible and safe therapy in patients with multiple organ failure.
- The ADVOS therapy was able to remove water-soluble and protein-bound toxic substances and to normalize and improve the blood composition in case of electrolyte disturbances or acid-base disorders.
- A trend towards mortality reduction in patients treated with the ADVOS device was observed. In this analysis the expected mortality according to baseline SOFA-Score was reduced from 80% to 60%.

Background

Despite the improvement in the management of critically ill patients, the mortality rate of patients with multiple organ failure (MOF) is high. Acute kidney injury, liver injury and respiratory failure might be present in more than 50% of the patients in the intensive care unit (ICU), either alone or in various combinations. In fact, a simultaneous MOF can lead to mortality rates of over 80% in patients with Sequential Organ Failure Assessment (SOFA)-score of 14 (i.e. ≥ 4 organ failure) or higher.

The Extracorporeal Multi Organ Support (EMOS)-Registry was conducted to collect data on real treatment conditions for patients for whom multi organ treatment with ADVOS (ADVanced Organ Support) albumin dialysis was indicated. The aim of the EMOS-Registry is to create recommendations for ADVOS multi treatments as well as identify suitable supportive and diagnostic measures.

This first report summarizes data on the patients included during the first two years after the initiation of the registry.

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Methods

This was a non-interventional, multi-center, non-randomized registry in post marketing surveillance. The ADVOS multi device was used for extracorporeal multiple organ support in accordance with its intended use. The registry included adult patients (i.e., ≥ 18 years of age) who required ADVOS treatment according to the indication for use and prescription of the treating physician. No exclusion criteria were defined.

Patient data were collated from patients receiving ADVOS treatment under routine conditions without study-specific interventions, diagnostic procedures, or assessments. Data were collected on clinical laboratory tests, health status, liver function, vital signs, and examinations.
Mortality rates 28 and 90 days after the first ADVOS treatment, adverse events, treatment parameters and abortions, were documented.

Results

Patients

Four clinical centers in Germany participated in the EMOS-Registry and recruited 118 patients with a median age of 60 (IQR: 45; 69), of whom 70 were male (59.3%). The patients had a median SOFA-Score of 14 (IQR: 11; 16) and a predicted mortality of 80%. The median number of failing organs was 3 (IQR: 2; 4).

The main baseline characteristics of the patients included in the study are shown in the table below:

Baseline characteristics	% of patients affected
Liver dysfunction/failure [%]	35% / 47%
Renal dysfunction/failure [%]	14% / 65%
Vasopressors [%]	78.8%
Mechanical ventilation [%]	65.3%
Acidemia (pH < 7.35) [%]	52.5%
Metabolic acidosis (HCO_3^- < 22 mmol/l) [%]	55.1%
Hypercapnia (pCO_2 > 45 mmHg) [%]	25.4%

ADVOS treatments

As shown in the table below, a total of 429 ADVOS treatment sessions were performed with a median of 3 (IQR: 1; 4) sessions per patient with a median duration of 17 (IQR: 6; 23) hours:

Total number of sessions	429
Duration 1st ADVOS treatment [h]	17 (6; 23)
Number of sessions/patient	3 (1; 4)
Duration of the session [h]	16 (10; 20)
Blood flow [ml/min]	120 (100; 150)
Concentrate flow [ml/min]	160 (160; 288)
Dialysate pH	7.89 (7.40; 8.50)
UF rate [ml/h]*	212 (70; 266)
UF volume [ml]**	3,140 (1,035; 4,950)

* UF rate includes volume corresponding to possible glucose, citrate, or calcium administration, which may be approximately 70-120 ml/h.

** Only data from 72 patients were documented.

Performance of the ADVOS therapy

Three main benefits have been observed with the ADVOS treatment, which confirm data already published from other preclinical trials and clinical experiences:

1. Reduction of protein-bound disease markers (e.g. bilirubin)
2. Removal of water-soluble substances (e.g. creatinine or BUN)
3. Correction of acid-base parameters (e.g. pH and HCO_3^-)

This reflects the possibility to simultaneously support 3 organs (i.e., liver, lung, and kidney) with the ADVOS system. The main disease markers significantly improved with the ADVOS treatment are shown in the following table:

Parameter	Before the 1st ADVOS multi treatment	After the 1st ADVOS multi treatment	p-value
Total bilirubin [mg/dl]	6.9 (2.5; 18.3)	6.5 (2.4; 15.1)	< .001*
BUN [mg/dl]	24 (15; 38)	17 (11; 26)	< .001*
Creatinine [mg/dl]	1.5 (0.9; 2.2)	1.2 (0.7; 1.9)	< .001*
pH	7.35 (7.26; 7.42)	7.42 (7.35; 7.46)	< .001*
HCO_3^- [mmol/l]	22.1 (16.9; 25.8)	25.8 (21.8; 29.0)	< .001*
Base Excess [mmol/l]	-3.5 (-9.2; 1.1)	1.7 (-3.1; 4.8)	< .001*

*Statistically significant difference

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Safety

Less than 6% of the treatments were aborted due to device errors, and only 13 clotting cases were described as adverse events related to the ADVOS therapy, none of them serious. A significant reduction in platelet count, hemoglobin and hematocrit was observed, which is known from renal replacement therapies and did not compromise the feasibility and safety of the therapy.

Outcome

In the EMOS-Registry, a mortality of 60.3% and 64.6% was documented at 28 and 90 days after the first ADVOS treatment session, respectively. The table below illustrates the observed mortality rate at each participating center compared to the expected mortality rate according to the median SOFA-Score immediately before the first ADVOS session in each patient. Among survivors lower SOFA-Scores in comparison to non-survivors were observed (11 vs 16), suggesting a better outcome when the ADVOS treatment is not used as a last line therapy.

Clinic	Predicted mortality	Documented mortality
Hamburg	89.7%	67.2%
Mainz	45.8%	42.9%
Essen	45.8%	18.2%
Weiden	89.7%	63.2%
Total	**80.0%**	**60.3%**

The authors conclude:

- The data summarized in this report provide real world evidence (RWE) on an emerging albumin dialysis device for multiple organ support.
- Due to a lack of consensus guidelines for the use of the ADVOS therapy, patients were probably treated too late.
- Data on removal of water-soluble and protein-bound substances, as well as acid-base correction correlate well with previous results.
- The small number of device-related adverse events highlights the safety of the therapy.
- A trend towards a reduction in mortality was observed in each of the participating sites.
- All the data provided in this report should be carefully interpreted due to the characteristics of patient registries.

We think that

In this first interim analysis, data from 118 patients in 4 different hospitals have been included. Patients received 429 ADVOS treatments, which corresponds to more than 6,800 hours of therapy. A trend that indicates an improvement in survival under the ADVOS therapy can be observed. In this analysis the expected mortality according to baseline SOFA-Score was reduced from 80% to 60%. It was confirmed that the therapy remains feasible and safe, and the results correlate well to those previously published. However, the 60% mortality remains high. Of course, this has to do with the fact that seriously ill patients were treated. In fact, at least 15 patients died before the end of the first session. The assessment which patient will not benefit from the treatment is one of the most problematic points, not only with the ADVOS therapy, but also with renal replacement or ECMO therapy. Although the ADVOS treatment can help at later stages (e.g. a patient with a SOFA-Score of 20 survived), an earlier start might be a more interesting approach.

As expected, included patients are very heterogenous. Therefore, a subgroup analysis should be performed in order to identify different sub-cohorts. Particularly interesting could be the case of patients with acid-base disorders. In this report, 52.5% of patients had acidemia, 25% elevated pCO_2 levels and 55% serum bicarbonate levels below commonly accepted physiological ranges. There is already data from 282 patients in 5 hospitals available, with more than 1,000 ADVOS sessions recorded. Thus, a new analysis should provide higher statistical relevance.

The ADVOS therapy offers support of liver, lung, and kidney along with acid-base balance correction and CO_2 elimination in a single device. This approach has been confirmed by the analysis.

Further details on the study protocol and the current status of the Registry can be found in the German Registry of Clinical Trials under the following identification number: DRKS00017068

If you have further questions or suggestions - please contact us at marketing@advitos.com.

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