CE 0123

ADACOLUMN, A GRANULOCYTE AND MONOCYTE / MACROPHAGE ADSORPTION APHERESIS DEVICE

Condition of storage: 1 to 30 °C
Sterilization: Steam sterilization at high vapor pressure

1. Intended Use and Performance
The Adacolumn is intended to perform selective leukocyte apheresis for the therapeutic removal of granulocytes and monocytes/macrophages from peripheral blood.

2. Content
Adacolumn contains 220 g of cellulose acetate beads bathed in physiological saline as the column adsorptive carriers.

3. Indications
3.1 Inducing of remission in patients with inflammatory bowel disease (active ulcerative colitis and Crohn's disease).

3.2 Suppressing of both subjective and objective symptoms in patients with rheumatoid arthritis in the inflammatory stage whose symptoms might be resistant to standard drug therapy.

3.3 Treatment of patients with ocular Behçet disease.

3.4 Treatment of patients with systemic lupus erythematosus (SLE).

3.5 Improvement of the clinical symptoms in patients with pustular psoriasis (PP).

4. Contraindications
Adacolumn must not be used in patients with a peripheral circulation count of less than 2.000 granulocytes per micro liter.
In patients with a granulocyte count below this limit, due to the pharmacological pre-treatment, Adacolumn can be used, if the granulocyte count is greater than 1.000/µL, under close monitoring. Studies in patients with SLE and comparable granulocyte count did not show a further decrease under the Adacolumn treatment.

5. Warning
5.1 Caution should be taken with patients suffering from or suspected of concomitant infections, as apheresis treatment may exacerbate symptoms.

5.2 Caution should be taken with patients who have a history of hypersensitivity to heparin (anticoagulant).

5.3 Caution should be taken with patients who have a low red blood cell count (RBC counts, under 300 x $10^4/mm^3$), severe dehydration (RBC counts, over 600 x $10^4/mm^3$), and hypercoagulable blood (fibrinogen over 700 mg/dL). Apheresis treatment should not be initiated until these conditions have normalized.

5.4 In patients who are receiving angiotensin converting inhibitors, blood pressure and heart rate should be closely monitored.

5.5 In patients with hepatic or renal failure, usefulness or harmfulness of Adacolumn treatment must be carefully assessed by the patient's physician.

5.6 Adacolumn treatment has not been fully investigated in elderly patients.

5.7 In patients with severe cardiovascular disease, usefulness or harmfulness of Adacolumn treatment must be carefully assessed by the patient's physician.

5.8 In patients with fever (body temperature over 38 °C; suspected infection) there may be an increased possibility of side effects associated with Adacolumn treatment.

5.9 In pregnant and lactating women the safety of Adacolumn treatment has not been investigated; therefore, Adacolumn should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In lactating women, a decision should be made on whether or not to discontinue nursing while undergoing Adacolumn treatment.

5.10 Adacolumn treatment has not been fully investigated in pediatric patients.

5.11 Patient's vital signs should be continuously monitored during apheresis treatment. If any abnormality is observed, the apheresis should be stopped and a physician called.

5.12 If a central venous catheter is to be used, be aware of the general complications associated with such a method, such as activation of the coagulation system, formation of emboli, pulmonary embolism, and clogging of the catheter.

5.13 Adacolumn is intended for single use only. DO NOT resterilize and/or reuse, due to microbiological and/or physicochemical hazards.

6. Data on Adverse Reactions
Out of 322 patients (UC, CD, RA and PP patients who participated in clinical trials), adverse events including abnormal values in clinical parameters were observed in 51 cases (15.8 %).

Adverse reactions

Classification	Event Name (patient number)
Circulatory organ	hypotension (1), palpitation (2), facial redness (1)
Other symptoms	fatigue (1), malaise (1), headache (6), dizziness/vertigo (2), nausea (1), pyrexia (1), myodesopsia-like symptoms (1), pain (1), feeling poorly (1), nasal congestion (mild) (1), rash on lower limbs (1), dizziness on standing up (2), chills (1), feeling of weakness (1), worsening of bullous pemphigoid (1), finding of shadows in the lungs (1)
Abnormal test values	GOT (4), GPT (4), cholesterol (1), urine protein (2), BUN (3), K (6), Na (1), Cl (2), Ca (2), total protein (10), albumin (8), albumin/globulin ratio (1), ALP (6), LDH (3), GGT (5), α_1-globulin (16), α_2-globulin (12), β-globulin (6), γ-globulin (2), transferrin (1), creatinine (1), serum iron (2), IgG (1), CH50 (3), C3 (3), C4 (1), C1q (2), out of normal range of granulocytes, monocytes, lymphocytes (4), platelets (3), hemoglobin (3), fibrinogen (2), RBC (1) and hematocrit (1)

In addition to the adverse reactions described in the above tables, vomiting, increase in blood pressure, hemolysis, hematuria, abdominal pain, chest pain, coughing, urticaria, low back pain, back pain, dyspnea, burning sensation, paresthesia, muscle spasms, lacrimation, pruritus, puncture site redness, anaphylactoid symptoms/shock and other signs or symptoms were reported as adverse reactions commonly induced by extracorporeal circulation. (If abnormal reactions occur, the apheresis treatment should be discontinued or other appropriate measures must be taken.)
Quincke's edema or other angioneurotic edema, deep vein thrombosis, thrombophlebitis and pulmonary embolism have also been reported. Special caution is required for patients with severe peripheral venous embolism since they are at risk of incidental cerebral infarction or pulmonary embolism.
Single cases of thrombocytopenia have been seen, all together with the use of heparin.

7. Essential Information for Adacolumn treatment
7.1 Apheresis time and flow rate
The Adacolumn system should be operated at a flow rate of 30 mL/min, duration of one apheresis treatment is 60 min. The investigated course of treatment is one apheresis per week for a period of 5 consecutive weeks.

7.2 Disposable products
The Adacolumn and circuit are for single use only (disposable).

7.3 Handling of Adacolumn
Adacolumn should only be used in an appropriate clinical setting.

7.4 It is necessary for the operator to carefully study the instruction for use before using the Adacolumn system. The medical staff must be given/shall have adequate training for operating the system.

7.5 Blood inflow and outflow should be established in suitable veins. There is no need for establishing a shunt or port system.

7.6 Adacolumn should be used under the supervision of a physician who has been fully versed in the condition of the patient.

7.7 Before Adacolumn treatment is initiated, the physician must evaluate the need and usefulness of the column against the risk of adverse reactions. If serious reactions occur, the apheresis should be discontinued and appropriate corrective measures taken.

7.8 Patients being treated with Adacolumn should be monitored. In particular, their vital signs (body temperature, blood pressure, pulse rate, respiration rate), blood coagulation time, WBC counts should be monitored. If abnormalities are observed during the treatment, the apheresis should be stopped and/or other appropriate actions taken.

8. Prior to starting the Apheresis treatment
8.1 Preparations
1) The package and the covering plastic sheet must be checked for signs of damage. Possible damage to the package of the circuits and needles should also be checked before use. If the packages for the Adacolumn, Adacircuit, or needles, are damaged, they should not be used.
2) Adacolumn should not be used past the expiry date.
3) Adacolumn should be removed from the plastic bag just before priming.
4) Care should be taken to avoid contamination when blood circuit lines are connected to Adacolumn.
5) The priming procedures should be carried out according to the operating procedures detailed in 8.3.
6) Foam or bubbles in the Adacolumn or the circuit lines can trigger blood coagulation. Therefore, they must be free from air bubbles and foams prior to apheresis.
7) If a leak is discovered during priming in the column or the circuit lines, the leaky component should be discarded.
8) Priming should be performed sufficiently, until the filling solution within the Adacolumn and circuit is fully replaced with fresh physiological saline.
9) To avoid contamination of components, Adacolumn and circuit should be used as soon as priming has been completed.
10) Adacolumn and circuit should not be left unused after being removed from the sterilized bag or after priming.
11) Caution should be taken to avoid contaminating blood during the apheresis or blood retrieving operation.

8.2 Necessary components
- 1 Adacolumn
- 1 Bag containing 1 L sterile saline
- 2 Bags containing 500 mL sterile saline
- 1 Bag containing 1 L sterile heparinized saline (4.000 I.U.)
- 1 Blood pump (Adamonitor)
- 1 Set of tubings (Adacircuit)
- 1 Infusion pump for the heparin application
- 1 Column holder (Adastand)
- Forceps (as necessary)
- Heparin (as necessary)
- 2 Needles (e.g.18 G)
- 1 Waste bag
- Waste containers for priming saline, sharps, blood, etc.

Caution: The instruction manual of the relevant components should be read carefully.

8.3 Preparation
8.3.1 Priming the apheresis unit
1) Suspend the 1 L saline bag on the stand.
2) Close clamp 1 of the blood inflow line and connect the blood inflow line with the saline bag.
3) Insert the pump tube into the pump and the pillow sensor into the pillow sensor unit (Fig.1).

8.3.2 Preparation of the blood outflow system
1) Connect the venous pressure monitor line with the venous pressure monitor (pressure monitor port).
2) Connect the end of the blood outflow line with the waste bag and suspend the bag on the stand.

8.3.3 Filling of the blood inflow line system
1) Open clamp 1 of the blood inflow line and the roller clamp of the extra infusion line. Fill the blood inflow line, the heparin infusion line, and the extra infusion line with saline. Fill the drip chamber of the extra infusion line up to approximately 90 % and close the roller clamp. Connect the infusion line with the 500 mL saline bag. Suspend this bag on to the stand.
2) Start the pump and fill air-free the remaining part of the blood inflow line.
3) Used Saline will be collected in sterile waste bag and

avoid contact with the waste container by using the holder.
4) Stop the pump.

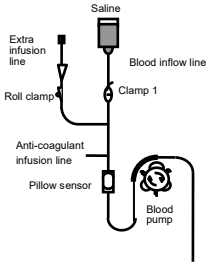

Fig.1

8.3.4 Connection of Adacolumn
1) Remove Adacolumn from the package and fit it to the column holder on the stand.
2) Remove the cap from the red-colored end of Adacolumn and connect the blood inflow line firmly to the Adacolumn. Place Adacolumn into the column holder so that the red connection is facing downward. Remove the cap on the blue-colored exit of Adacolumn and connect the blood outflow line (Fig.2).
Please note: The direction of flow is from the lower end of the column towards the upper end, as indicated by the arrow on the column.

8.3.5 Washing of the Adacolumn and circuit
1) Let approximately 1 L saline run through Adacolumn and the circuit at a flow rate of 100 mL/min by starting the pump. Remove the air from the column by shaking and rotating Adacolumn.
2) Fill the air trap chamber with saline up to a level of approximately 80 % by opening clamp 3 and the cap at the end of this line. When the drip chamber is filled up to 80 %, close clamp 3.
3) Once the saline is nearly exhausted, stop the pump. Replace the empty saline bag by the bag with the 1 L heparinized saline. Start the pump at a flow rate of 100 mL/min.
Running the pump will replace the standard saline in the column and the flow lines with heparinized saline.
Occasionally rotate and shake the column to ensure adequate priming of the column with heparinized saline and complete elimination of the air from Adacolumn and Adacircuit.
Please note:
- Ensure that all the priming heparin saline flows into the waste bag.
- Make sure that the heparin infusion line is also primed with heparinized saline by opening the cap of this line.
- Ensure that all air bubbles are eliminated from the column and the whole tube system when following chapter 8.3.5.
- If necessary, adjust the liquid surface by filling the air trap (drip chamber) to approx. 80 % as described in chapter 8.3.5.

4) Insert the blood outflow line into the air sensor and into the clamper.
5) After most of the heparinized saline has been dispensed, stop the pump and close clamps 1 and 2.

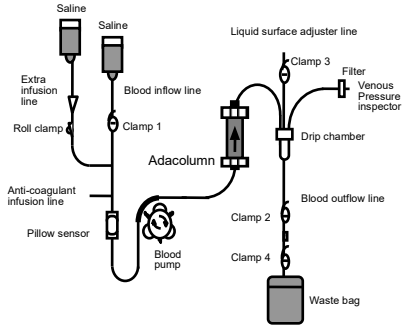

Fig.2

8.4 Leakage test
1) Set the upper limit of the venous pressure to 240 mmHg as described in the manual of the monitor or pump. Close clamp 2 at the end of the blood outflow line.
2) Run the pump with a flow rate of 30 mL/min until a venous pressure of approximately 200 mmHg has been reached. Stop the pump.
3) Ensure that the venous pressure level remains steady at approximately 200 mmHg and there is no leakage in the system.
4) Open clamp 2 of the blood outflow line clamp and as a consequence the venous pressure should decrease.
5) Close clamp 1 of the blood inflow line and clamp 2 of the blood outflow line.

8.5 Procedures for the apheresis
1) A venous access to a vein of the right and the left arm should be established by a physician or a well-trained nurse under observation by a physician, using an 18 G needles (or a similar adaptation).
2) Connect the blood inflow line and the blood outflow line to the venous access established above (Fig.3). Alternatively, it is possible to connect the blood outflow line to the venous access only when the blood reaches the end of the blood outflow line.

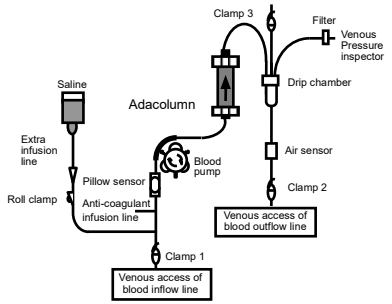

Fig.3

3) Make sure that clamps 1 and 2 are open and start running the pump at a flow rate of 30 mL/min for 60 min. Adjust the upper and lower limit of the venous pressure monitor as close as possible to the actual working pressure during the apheresis.
4) Subsequently, a bolus dose of heparin should be administered, followed by continuous infusion of heparin via the heparin infusion line.
The amount of anticoagulant necessary may vary according to patients' condition (weight, disease, sensitivity to anticoagulant, etc.). The attending physician should assess what is the appropriate dosage. If any abnormalities, caused by excessive or insufficient volume of anticoagulant, are observed during the apheresis, appropriate measures should be taken immediately.
Please note:
- Patients should be observed for the duration of the treatment. If an abnormality is observed, the treatment should be stopped or the flow rate reduced under the guidance of the responsible physician.
- Flow rate and the pressure of the blood inflow line and venous pressure should be monitored for the duration of treatment, as indicated by the fault detection system of the Adamonitor (optical and acoustical alarm).
- In case of access problems the extra infusion line facilitates an infusion without the necessity of interrupting the apheresis.

8.6 Procedures for returning residual blood after apheresis
1) Stop the blood pump after termination of the apheresis time.
2) Close the clamp on the blood inflow line (clamp 1), remove the inflow line from the patient and connect it to a bag containing 500 mL saline. Invert the column, so that the red-colored end is facing upward.
3) Open clamp 1 and then run the pump at a flow rate of 30 mL/min. Re-transfuse the extracorporeal blood by replacing the blood with saline.
4) Once the blood in the Adacolumn has been replaced by saline, stop the pump. Close the clamp on the blood outflow line (clamp 2) and remove this line from the patient.
5) Be careful to avoid personal contamination when disconnecting the circuit and the column.
Caution: Ensure that the blood outflow line is removed from the patient before disconnecting the flow lines from the Adamonitor.

9. Conditions of storage and transport
The storage conditions for Adacolumn are clearly indicated on the product package. The column should be protected from direct sunlight, heat, and not stored in places where the temperature is likely to fall to freezing point or lower.
The storage temperature is 1 to 30 °C.
During transport, the package must not be subjected to trauma, violent vibrations or shock.

10. Warranty and Liability
JIMRO Co., Ltd. warrants Adacolumn is manufactured in accordance with their specifications and in compliance with good manufacturing practices, ISO 13485, applicable industry standards, and regulatory requirements. In the event that a unit is found to be defective (damaged or malfunctioning) due to manufacturing or packaging processes, the unit will be replaced at no extra cost.
The manufacturer does not accept responsibility for personal or material damage as a result of misuse of this product.
The company (**JIMRO** Co., Ltd.) is not liable for any damage arising from the reuse of the single-use disposable Adacolumn or for use in indications other than those recommended for Adacolumn.

11. Manufacturer
JIMRO Co., Ltd.
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Authorized Representative

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12. If an adverse event (accidents and other incidents and near-accidents) or product quality complaints should occur this should be reported as soon as possible to the affiliates of the distributor, Adacyte Therapeutics, S.L.

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