Chapter 26
Rheumatoid Arthritis and Collagen Diseases

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Main Points

Rheumatoid Arthritis

- Therapeutic apheresis is used for the treatment of rheumatoid arthritis that is resistant to pharmacologic treatments.
- Therapeutic apheresis is performed to remove infiltrating activated T cells, B cells, neutrophils, and monocytes in patients with rheumatoid arthritis.
- Filtration leukocytapheresis (LCAP) has dose-dependent effects.

Malignant Rheumatoid Arthritis

- Therapeutic apheresis is used in addition to pharmacotherapy with glucocorticoids or immunosuppressive agents.

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- Immunocomplex (IC) and activated complement are removed by therapeutic apheresis.
- Plasma exchange (PE), double filtration plasmapheresis (DFPP), cryofiltration, or immunoadsorption plasmapheresis (IAPP) are chosen based on the disease status of each patient.

Systemic Lupus Erythematosus

- Therapeutic apheresis therapy is used for the treatment of systemic lupus erythematosus (SLE) that is associated with severe organ damage despite treatment with glucocorticoids or immunosuppressive agents.
- Therapeutic apheresis removes IC and autoantibodies.
- Plasma exchange (PE), double filtration plasmapheresis (DFPP), cryofiltration, or immunoadsorption plasmapheresis (IAPP) are chosen based on the disease status of each patient.

Antiphospholipid Syndrome

- Therapeutic apheresis is used for the treatment of antiphospholipid syndrome (APS) with severe thrombotic complications leading to multi-organ damage.
- PE or IAPP is performed to remove autoantibodies and improve disorders of thrombosis and fibrinolysis.
- IAPP is repeated once a week until delivery in pregnant APS patients with recurrent spontaneous abortion despite the use of antiplatelet or anticoagulant therapy.

ANCA-Associated Vasculitis

- Therapeutic apheresis is performed for patients with ANCA-associated vasculitis that is resistant to a combination of glucocorticoids and immunosuppressive agents and is complicated with rapidly progressive glomerulonephritis (RPGN) or pulmonary bleeding.
- PE removes autoantibodies.

26.1 Rheumatoid Arthritis

26.1.1 Introduction

LCAP is approved as a treatment for patients with rheumatoid arthritis (RA) who are resistant to multidrug therapy [glucocorticoids, disease modifying antirheumatic drugs (DMARDs)].

26.1.2 Targets and Pathology

26.1.2.1 Targets

Activated leukocytes are the target of LCAP for the treatment of RA.

26.1.2.2 Pathology

Patients with RA present with polyarthritis caused by an immunologic disorder. Naïve T cells differentiate into memory T cells after interaction with certain antigens, migrate to joint synovium, and activate monocytes. Activated monocytes secrete various cytokines, consequently joints were damaged.

26.1.3 Efficacy

The efficacy of LCAP therapy is maintained for about 2 months. The American College of Rheumatology (ACR) core set and the European League Against Rheumatism (EULAR) 28-joint disease activity score (DAS28)-C-reactive protein (CRP) were used for assessment of efficacy. When 3 L of blood were filtered with a leukocyte removal column, 60–70 % of the patients had an ACR 20 % response and 20–30 % of the patients had an ACR 50 % response [1]. When 5 L of blood were filtered with a leukocyte removal column, 78 % of the patients had an ACR 20 % response and

44 % of the patients had an ACR 50 % response. Moderate or good DAS28-CRP responses were achieved in 50–60 % of the patients [2–4].

26.1.4 Methods

26.1.4.1 Insurance Restriction

LCAP is approved for the treatment of RA in patients with more than six swollen joints, erythrocyte sedimentation rate (ESR) of more than 50 mm/h, or CRP level more than 3 mg/dL, associated with systemic symptoms such as fatigue, low-grade fever, and acute progressive polyarthritis, and resistance to multi-drug therapy. The approved schedule of LCAP treatments is once a week for 5 consecutive weeks.

26.1.4.2 Modality

CS-100 Cellsorba® is a leukocyte removal column equipped with a fiber filter for the filtration of a total of 3 L of blood. CS-180 Cellsorba® is used for the filtration of a total of 5 L of blood.

26.1.4.3 Frequency

LCAP is performed once a week for 5 consecutive weeks.

26.1.4.4 Response Indicators

CRP, ESR, and matrix metalloproteinase-3 (MMP-3) levels are used as indicators of response to treatment.

26.1.5 Points to Note

26.1.5.1 Start-Up

LCAP should be used with caution in patients with leukopenia (white blood cells <3,000/mm^3), anemia (hemoglobin

<10 g/dL), or thrombocytopenia (platelets $<100 \times 10^3/mm^3$) because the procedure may induce cytopenia. Angiotensin-converting enzyme (ACE) inhibitors should be discontinued more than 1 week prior to starting LCAP, because of the risk of hypotension induced by LCAP in patients taking ACE inhibitors, probably due to an accumulation of bradykinin.

26.1.5.2 Other Complications

Other potential complications of LCAP include hypotension, nausea, and transient anemia, but these generally are not severe.

26.2 Malignant Rheumatoid Arthritis

26.2.1 Introduction

Malignant rheumatoid arthritis (MRA) is RA complicated with vasculitis. The symptoms of vasculitis include cutaneous ulcers/infarctions/necrosis, mononeuritis multiplex, pericarditis, coronary vasculitis, pulmonary vasculitis, episcleritis, and other symptoms of systemic vasculitis, which often are refractory and severe. Apheresis therapy for MRA is covered by insurance in Japan.

26.2.2 Targets and Pathology

26.2.2.1 Targets

IC, complement, and cytokines are targets of apheresis in patients with MRA.

26.2.2.2 Pathology

MRA is associated with severe extra-articular vasculitis in addition to the typical manifestations of RA. Circulating IC composed of rheumatoid factor (RF) and antigen is deposited on vascular walls, inducing complement and neutrophil activation, increased production of cytokines, and tissue damage.

26.2.3 Efficacy

Apheresis therapy has been reported to be effective for the treatment of MRA; however, there have been no randomized controlled trials of its use in patients with MRA.

26.2.4 Methods

26.2.4.1 Insurance Restriction

Therapeutic apheresis is approved in Japan for patients with MRA and severe vasculitis that is resistant to standard treatments. DFPP or IAPP is performed once a week or less frequently. Apheresis can be repeated according to its efficacy.

26.2.4.2 Modality

Only DFPP or IAPP are covered by insurance, but PE and cryofiltration are also used in the clinical setting. PH-350 Immusorba®, a column with phenylalanine ligand, is used for IAPP.

26.2.4.3 Frequency of Treatment

Approximately 2–3 L of plasma are processed during each treatment session. Initially, apheresis is performed two or three times per week. The treatment interval may be extended to two to four times per month according to clinical efficacy. This strategy is included in the 2002 guideline for the treatment of refractory vasculitis [5].

26.2.4.4 Response Indicators

CRP, ESR, complement, white blood cells (WBCs), IC (Clq), and RF are used as indicators of response to therapy.

26.2.5 Points to Note

Note
Recently, LCAP has been reported to be effective for cutaneous ulcers in patients with MRA.

26.3 Systemic Lupus Erythematosus

26.3.1 Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease caused by immunologic abnormalities; it is diagnosed according to the diagnostic criteria proposed by the ACR. Therapeutic apheresis is used to treat patients with SLE that is resistant to multi-drug therapy or who have severe organ dysfunction.

26.3.2 Targets and Pathology

26.3.2.1 Targets

IC and auto-antibodies [anti-double-strand (ds) DNA antibodies, etc.] are targeted for removal in patients with SLE.

26.3.2.2 Pathology

Environmental factors (e.g., ultraviolet light, stress, infection, estrogen) in addition to the presence of susceptibility genes (e.g., *FCGR2A*, *PTPN22, PDCD1*) trigger the development of the pathogenic autoantibodies and IC in patients with SLE. Autoantibodies and IC adhere to vessel walls, promoting complement activation, and cytokine production, resulting in tissue damage.

26.3.3 Efficacy

A randomized controlled trial (RCT) compared a standard-therapy regimen of glucocorticoids and oral cyclophosphamide (CY) with a regimen of standard therapy plus PE for proliferative lupus nephritis (LN) [6]. Treatment with PE plus a standard regimen was associated with a significantly more rapid reduction in serum concentrations of antibodies against dsDNA and cryoglobulins during the initial weeks of therapy; however, the combined treatment did not result in improved long-term clinical outcomes at 300 weeks [6]. The addition of PE to glucocorticoid therapy and intravenous CY (IVCY) was also effective for inducing faster remission in patients with proliferative LN, but it was not superior to conventional therapy at long-term follow-up [7, 8]. However, in a 5-year retrospective evaluation, the combination of PE and IVCY resulted in superior LN complete remission rates and minimized the risk of relapse to impaired renal function compared with results for PE or IVCY [9].

A recent small RCT comparing PE and IAPP as adjunctive therapy reported that both treatments were equally well tolerated and equally effective in patients with proliferative LN [10]. PE and synchronized PE-IVCY have been shown to be effective for the inhibition of early brain damage in patients with neuropsychiatric SLE (NPSLE) [11]. Table 26.1 shows the manifestations in patients with SLE that may respond to therapeutic apheresis [12].

26.3.4 Methods

26.3.4.1 Insurance Restriction

Therapeutic apheresis is approved for the treatment of patients with glucocorticoid-resistant SLE with hypocomplementemia (CH50 ≦20 U or C3 ≦40 mg/dL), extremely high anti-dsDNA antibody levels, and proliferative LN or NPSLE. Patients are treated with DFPP or IAPP a maximum of four times a month. Patients with SLE complicated by thrombotic thrombocytopenic purpura (TTP) can be treated with PE a maximum of three times a week for 3 months.

Table 26.1 Clinical manifestations of SLE effected by therapeutic apheresis

1	Active lupus nephritis (diffuse prolipherative glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome etc.)
2	Neurologic manifestations (seizures, dystonia, psychosis, encephalopathy etc.)
3	Serositis (pericarditis, pleuritis etc.)
4	Cutaneous lesions (ulcers etc.)
5	Interstitial pneumonitis pulmonary bleeding
6	Generalized vasculitis
7	Thrombocytopenia
8	Hemolytic anemia, aplastic anemia
9	Hemophagocytsis
10	Thrombotic thrombocytopenic purpura
11	Antiphospholipid syndrome
12	Hereditary angioneurotic edema
13	Habitual abortion

26.3.4.2 Modality

(a) PE is used for patients with complicated TTP, hemophagocytosis, or multiple organ failure.
(b) DFPP primarily is used for patients with secondary cryoglobulinemia, hyperviscosity, cutaneous lesions, or neurologic symptoms.
(c) IAPP can be performed with the Cellsorba® column, which has a dextran sulfate ligand, or with the Immusorba® column, which has a phenylalanine ligand. The Cellsorba® column primarily removes IC and anti-DNA antibodies via an electrostatic interaction, while the Immusorba® column primarily removes, anti-cardiolipin antibodies via a hydrophobic interaction. IAPP can be used for younger patients or pregnant women, because it requires no blood products and is not associated with transfusion-transmitted infections.

(d) Cryofiltration is mainly used for patients with secondary cryoglobulinemia.

26.3.4.3 Frequency

Approximately 2–4 L of plasma are processed during each treatment session. Apheresis is initially performed two or three times a week. The treatment interval may be extended to two to seven times per month, according to clinical efficacy of the treatments.

26.3.4.4 Response Indicators

Complement, anti-DNA antibodies, IC (C1q), CRP, and ESR are indicators of response.

26.3.5 Points to Note

Refer to each section on apheresis.

Note: Prevention of Neonatal Conduction Failure by IAPP
Neonatal lupus is caused by transplacental passage of maternal anti-SS-A and/or anti-SS-B antibodies. The frequency of congenital heart block in infants born to mothers with these antibodies was 2 %. The maternal IgG antibodies gain access to the fetal circulation via active placental transfer (which increases after week 16 of gestation) after the fetal heart has reached functional maturity (by week 16). Damage to the cardiac electroconduction system can progress through various stages to complete atrioventricular block, most often detected between 18 and 24 weeks gestation. To prevent fetal conduction failure, pregnant women with highly elevated levels of SSA-antibodies and/or a positive history of clinical complications may be treated with IAPP [13].

26.4 Antiphospholipid Syndrome

26.4.1 Introduction

APS is characterized by the presence of antiphospholipid antibodies (aPL) and thrombosis; it is diagnosed according to the APS classification criteria [14]. Therapeutic apheresis is performed in patients with treatment-resistant catastrophic APS (CAPS), which is characterized by multiple vascular occlusive events, usually affecting small vessels and developing over a short period of time. Apheresis is also performed in patients who have had recurrent spontaneous abortions.

26.4.2 Targets and Pathology

26.4.2.1 Targets

Apheresis for APS targets aPL and cytokines.

26.4.2.2 Pathology

Antiphospholipid antibodies are directed against plasma proteins bound to anionic phospholipids and include anticardiolipin antibodies, antibodies to β2 glycoprotein-I (β2 GPI), lupus anticoagulant (LA), and others. The antiphospholipid antibody β2 GPI dimmer activates the complement cascade, induces adhesion molecule expression, and activates monocytes and platelets, resulting in the release of proinflammatory mediators and induction of thrombosis.

26.4.3 Efficacy

Therapeutic apheresis for APS has not been studied in RCTs. CAPS is associated with a 50 % mortality rate; however, the mortality rate has been reduced to 30 % over the past 5 years by intensive therapies including PE and treatment with anticoagulants, glucocorticoids, and intravenous immunoglobulin

[15]. Pregnant women with APS often are treated prophylactically with a combination of heparin and low-dose aspirin or aspirin, but live births cannot be achieved in 20–30 % of patients. Adding prophylactic treatment with PE or IAPP may improve the live birth rate [16, 17].

26.4.4 Methods

26.4.4.1 Insurance Restriction

Therapeutic apheresis is not approved for APS.

26.4.4.2 Modality

(a) IAPP : Cellsorba® with dextran sulfate ligand is used for IAPP.
(b) DFPP
(c) PE

26.4.4.3 Frequency

PE is preferentially used for patients with CAPS. Treatments are initially given two or three times a week. The treatment interval is extended to two to four times per month according to the clinical response.
IAPP is used for pregnant women with APS. IAPP is started in the sixth to eighth week of pregnancy and repeated once a week until delivery.

26.4.4.4 Response Indicators

Platelet count and aPL levels are used as indicators of response.

26.4.5 Points to Note

Patients with thrombocytopenia and a bleeding tendency should be treated with nafamostat mesylate (Futhan®) for anticoagulation during apheresis.

For pregnant patients treated with IAPP, the blood flow rate should be less than 50 mL/min to maintain the placental blood flow.

26.5 ANCA-Associated Vasculitis

26.5.1 Introduction

ANCA-associated vasculitis (AAV) involves small- to medium-sized blood vessels. AAV is classified into three heterogeneous syndromes: granulomatosis with polyangiitis (GPA); microscopic polyangiitis (MPA); and the Churg–Strauss syndrome (CSS). The relevant target antigens of ANCA are proteinase 3 (PR3) and myeloperoxidase (MPO). Antibodies specific for PR3 and MPO are called PR3-ANCA and MPO-ANCA, respectively. MPO-ANCA is detected in 50–70 % of patients with MPA and 40–50 % of patients with CSS. PR3-ANCA is detected in 80–90 % of patients with GPA. Therapeutic apheresis is used in elderly patients with associated RPGN or pulmonary bleeding, who are at high risk for infections and are intolerant to standard immunosuppressive treatments.

26.5.2 Targets and Pathology

26.5.2.1 Targets

The targets of apheresis for AAV are autoantibodies (e.g., ANCA, anti-LAMP2 antibodies, antiplasminogen), activated leukocytes, activated macrophages, complement, adhesion molecules, cytokines, and chemokines.

26.5.2.2 Pathology

Environmental factors (infection, drugs etc.) in patients with susceptibility genes (e.g., *PTPN22, PDCD1, CTLA4*) trigger the activation of neutrophils, monocytes, and other immune cells, accelerating the secretion of inflammatory mediators

such as TNFα and IL-1. MPO and PR3 are transported from primary cytoplasmic granules to the cell membrane during neutrophil activation and bind to ANCA. Binding of ANCA to endothelial cells increases adhesion molecule expression and cytokine production, resulting in damage to the endothelial cells of the vessel wall.

26.5.3 Efficacy

The efficacy of PE for MPA has been demonstrated in clinical trials. The MEPEX trial in MPA patients with severe renal dysfunction (serum creatinine >5.7 mg/dL) showed that the addition of PE versus intravenous methylprednisolone to oral cyclophosphamide and glucocorticoids was associated with a significantly better renal recovery rate at 3 and 12 months [18]. However, there was no difference in survival rate and renal survival rate between the two treatments [18]. Two subsequent meta-analyses, including the MEPEX trial, revealed that PE as adjunctive therapy significantly reduced the risk of endstage kidney disease at 12 months, but did not improve the survival rate [19, 20]. The ongoing multicenter PEXIVAS trial is evaluating the effectiveness of PE in patients with moderate renal failure (<50 mL/min estimated glomerular filtration rate).

An RCT was performed to evaluate the effectiveness of PE for patients with GPA, including those with moderately decreased renal function or renal failure [21]. The patients were randomized to treatment with or without initial PE in addition to oral cyclophosphamide and glucocorticoids; after 3 months they underwent a second randomization to continue cyclophosphamide or switch to cyclosporine A for 9 months. The renal survival rate and survival rate were significantly better in the PE group at 3 months. However, in the long-term follow-up of at least 5 years, the renal survival rate and survival rate were not significantly different. With regard to CSS, there have been no reports since the publication of a late 1990s study that failed to show the effectiveness of PE for CSS.

26.5.4 Methods

26.5.4.1 Insurance Restriction

Therapeutic apheresis is not approved for AAV.

26.5.4.2 Modality

(a) PE
(b) DFPP
(c) LCAP/GCAP

26.5.4.3 Frequency

PE is preferentially used for patients with AAV. It is initially performed two or three times a week. The treatment interval can be extended, according to the clinical response. DFPP is used for maintenance therapy.

26.5.4.4 Response Indicators

ANCA titers and CRP levels are used as indicators of response to therapy.

26.5.5 Points to Note

Refer to each section on apheresis.

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