Chapter 10
Mesenchymal Stem Cell and Hematopoietic Stem Cell Transplantation for Vasculitis

Lianming Liao and Yongquan Gu

Vasculitis is a heterogeneous group of pathologies characterized by inflammation and necrosis of vessel walls. More than 30 kinds of vasculitis have been reported according to an international consensus [1]. It may present as a primary process or as a complication of some other pathologic conditions. Primary vasculitis is relatively rare but is associated with significant morbidity and mortality, particularly if diagnosis is delayed. Pathologic conditions, such as collagen-vascular, rheumatic, infectious, or malignant diseases, may sometimes be accompanied by vasculitis.

The cause of vasculitis is still mostly unknown. Risk factors of vasculitis include geography, age, ethnicity, gender, and genetic and environmental factors. For example, Behcet disease is more common in countries along the ancient Silk Route [2]. Takayasu disease is more prevalent in South Asian countries and in children less than 5 years of age, with a female to male ratio of 9 to 1 [3]. Giant cell arteritis (GCA) and granulomatosis with polyangiitis (GPA) occur predominantly in the White population [4]. Studies have found the association of hepatitis B with polyarteritis nodosa (PAN), hepatitis C with mixed cryoglobulinemia, and silica dust with pauci-immune vasculitis [5].

Selection of treatment regimens depends on the type and the severity of vasculitis. Treatment generally includes three components: remission induction, remission maintenance, and monitoring. Glucocorticoids are the first-line treatment for vasculitis and may be used with or without immunosuppressive agents.

A variety of immunosuppressive medications, newer biologic agents, and new treatment regimens have been introduced in the recent years to address this unmet

L. Liao
Department of Laboratory Medicine, Fujian Medical University Union Hospital, Fuzhou, China

Y. Gu (✉)
Department of Vascular Surgery, Xuan Wu Hospital of Capital Medical University, Beijing, China

T. P. Navarro et al. (eds.), *Stem Cell Therapy for Vascular Diseases*,
https://doi.org/10.1007/978-3-030-56954-9_10

medical need, which include methotrexate, azathioprine, mycophenolate, cyclophosphamide, rituximab, intravenous immunoglobulin, and plasma exchange.

10.1 Mesenchymal Stem Cell Characteristics

Mesenchymal stem cells (MSCs), also known as mesenchymal stromal cells, are adult fibroblast-like cells that are adherent to the surface of culture plastic and capable of differentiation into adipocytes, chondroblasts, and osteoblasts. MSCs were originally isolated from bone marrow and later from a variety of tissues, such as adipose tissue, tooth pulps, periodontal tissue, umbilical cord, and placenta. In 2006, the International Society for Cellular Therapy recommended a set of minimal criteria to uniformize MSC characteristics [6].

The immunoregulatory properties of different types of MSCs have been well studied. MSCs exhibit capabilities such as prompting T-cell expansion to a regulatory phenotype, shifting macrophages to anti-inflammatory and immunosuppressive M2 phenotypes, and inhibiting dendritic cells maturation. The functions of NK cells, B cells, and memory T cells are suppressed as well [7–10]. The immunoregulatory properties of MSCs have been harnessed to treat autoimmune diseases.

Importantly MSCs may migrate to the damaged tissue and secrete a number of cytokines and chemokines through paracrine, endocrine, and exosome mechanisms [11]. The secreted cytokines and chemokines include vascular endothelial growth factor, stromal cell-derived factor-1, fibroblast growth factor, insulin-like growth factor, keratinocyte growth factor, hepatocyte growth factor, and vascular endothelial growth factors. In addition MSCs can transfer mitochondria, functional proteins, mRNAs and microRNAs into the damaged cells via microvesicle-dependent cell-to-cell communication. These all help correct the course of injury and regulate the local immune response.

After numerous in vitro and in vivo preclinical studies, autologous and allogeneic MSCs have been applied in a range of immune-mediated conditions, including graft versus host disease, Crohn's disease, multiple sclerosis, refractory systemic lupus erythematosus, and systemic sclerosis. Hypothetically MSCs transplantation may be beneficial for vasculitis by reducing inflammation, inducing prosurvival genes, and downregulating pro-apoptotic genes.

10.2 Hematopoietic Stem Cell Characteristics

Vasculitis may develop into a chronic inflammatory disorder and presents as a relapsing-remitting illness. Therefore, an ideal therapeutic goal is to switch off the inflammation and halt disease progression. Immunoablation and reconstitution of the immune system via hematopoietic stem cell transplantation (HSCT) is a more

intensive approach than immunosuppressants. This approach can switch off the autoreactive, inflammatory process and restoring self-tolerance.

Immunoablation and HSCT have been practiced as a therapy for various autoimmune diseases, including systemic sclerosis, systemic lupus erythematosus and Crohn's disease, for several decades [12]. The purpose of HSCT in the treatment of autoimmune diseases is to allow delivery of intensive chemotherapy or chemoradiotherapy in order to cause severe immunosuppression or even total immunoablation. Infused stem cells then repopulate the patient and give rise to new hematopoiesis and a complete immune system. In allogeneic HSCT, the immune system is provided by the donor cells.

10.3 HSP IgA vasculitis (Henoch–Schönlein purpura)

IgA vasculitis is the new term for Henoch-Schönlein purpura (HSP) and is the commonest systemic vasculitis in childhood [13]. It is defined in the latest Chapel Hill nomenclature (2012) as vasculitis with IgA1-dominant immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles). HSP is associated with glomerulonephritis which is indistinguishable from IgA nephropathy [13]. The most important prognostic factor for poor outcome is renal involvement. Children with microscopic hematuria without renal dysfunction or proteinuria and those with non-persistent mild-moderate proteinuria usually do not require any specific therapeutic intervention other than a "watchful waiting approach" since the prognosis is excellent. HSP-associated arthritis responds well to non-steroidal anti-inflammatory drugs [14]. Severe skin lesions and gastrointestinal involvement could require a short course of an oral corticosteroid. However controlled studies have shown that corticosteroids do not prevent renal disease [15]. Immunosuppressants including azathioprine, MMF, or intravenous cyclophosphamide may be considered as second-line agents.

Mu et al. reported a 12-year-old boy treated with cord-derived mesenchymal stem cells for liver cirrhosis and refractory HSP [16]. The patient presented with purpura in the skin of the bilateral lower limbs and thrombocytopenia. He had chronic itching skin rash for the past 2 years and received prednisone treatment. At admission, ultrasonography of the abdomen showed diffuse lesions and multiple solid nodules in the liver. Abdominal computed tomography showed hepatomegaly with small nodules under the right lobe of the liver and enlarged splenic sinuses. The patient received MSC transplantation for eight times in 2 months. Then methylprednisolone was tapered off after 1 month with disappearance of skin rash and normalization of platelet count and liver transaminase level. Abdominal ultrasound showed fewer round nodules in the liver and decreased spleen size. Follow-up at 6 months revealed there was no skin rash, and no nodules in the liver and the platelet count remained normal. This is a rare case of HSP with thrombocytopenia and liver cirrhosis that responded to MSC treatment.

10.4 ANCA-Associated Vasculitis (AAV)

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) comprises granulomatosis with polyangiitis (GPA, previously referred to as Wegener's granulomatosis), microscopic polyangiitis (MPA), eosinophilic granulomatous polyangiitis (EGPA), and renal-limited vasculitis. GPA may present sequentially as a predominantly granulomatous form or as an acute small vessel vasculitic form. These two presentations may also co-exist.

There is a rapid expansion in the therapeutic agents for AAV, including purine, pyrimidine, mycophenolate mofetil, leflunomide, 15-deoxyspergualin, immunoglobulin, TNF-alpha antagonism infliximab, IL-5 antagonism mepolizumab, rituximab (for induction of B-lymphocyte depletion), alemtuzumab (for induction for T-lymphocyte depletion), and antithymocyte globulin (for induction for T-lymphocyte depletion). Due to the fact that AAV is associated with abnormal immune function, immunoablation, and HSCT to switch off the autoreactive, inflammatory process of the patients is reasonable.

In a phase I–II trial of autologous peripheral blood stem cell transplantation for refractory autoimmune disease, one patient with GPA was enrolled [17]. The patient was male and 21 years old. He has been treated with corticosteroids, cyclophosphamide, and cyclosporin A before. Peripheral blood stem cells were mobilized with granulocyte colony-stimulating factor after administration of cyclophosphamide (2 g/m^2) for 2 days. 5×10^6 CD34$^+$ cells/kg were collected by apheresis and infused. After hematopoietic reconstitution, the size of the left orbital granuloma decreased substantially and the exophthalmos was reduced. Monthly steroid pulse therapy was discontinued. At 3 months after transplantation serum proteinase 3 (PR3)-anti neutrophil cytoplasmic antibodies (ANCA) level decreased to 39 IU/ml, which was 72 IU/ml before transplantation. However, it increased again to 157 IU/ml at 12 months. Thus high dose cyclophosphamide with autologous peripheral blood stem cell transplantation is promising. However why GPA relapses in the long-term remains unclear.

Additionally, in an international meeting taking place in 2000, four patients with GPA receiving autologous peripheral stem cell transplantation were reported. All patients had an initially complete response, but two patients relapsed at 2.3 and 3 years, respectively, which was easier to control [18]. However the detailed treatment protocol was not described.

Secondary autoimmune diseases are a known complication after autologous stem cell transplantations [19]. Indeed, p-ANCA-associated vasculitis was induced in a 43-year-old man who had received autologous stem cell transplantation for systemic sclerosis. The patient received a conditioning regimen with cyclophosphamide and antithymocyte globulin before receiving cyclophosphamide and granulocyte colony-stimulating factor mobilized stem cell transplantation. He responded well to HSCT. One year and 4 months after transplantation mild erythrocyturia without acanthocytes and proteinuria were seen on routine urinalysis. During the following year, erythrocyturia increased to 131 erythrocytes/μl and protein

excretion to 628 mg/g creatinine. Renal biopsy revealed mild global and focal-segmental sclerosing and focal-segmental proliferative glomerulonephritis that supported the diagnosis of p-ANCA-positive glomerulonephritis. The patient responded well to Rituximab treatment.

10.5 Kawasaki Disease (KD)

Kawasaki disease (KD) is a systemic inflammatory disease that predominantly affects medium and small-sized arteries. The principal clinical features of KD include polymorphous exanthema and acute non-purulent cervical lymphadenopathy, which are manifestation of abnormal immune function [20].

Early recognition and treatment of KD with aspirin and intravenous immunoglobulin (IVIG) are crucial. However, IVIG resistance has been reported in up to 20% of cases [21]. Other treatments include corticosteroids and corticosteroids plus IVIG. In some case report, anti-TNF-α, anakinra, plasmapheresis, and immunoglobulin plus ciclosporin were shown to be effective [22].

Most recently Uchimura et al. evaluated if adipose-derived MSCs could suppress KD-associated vasculitis in a *Candida albicans* water-soluble fraction (CAWS)-induced severe coronary arteritis. *Candida albicans*-derived substances, such as *C. albicans* water-soluble fraction (CAWS), induce coronary arteritis similar to KD in mice [23]. Mice were treated with intravenous MSCs or phosphate-buffered saline. On day 29, the mice were sacrificed. MSC infusion significantly inhibited coronary arteritis and decreased the levels of pro-inflammatory cytokines IL-1β, IL-12, IL-17, RANTES, INF-γ, and TNF-α. Most importantly MSC infusion improved animal survival. These findings highlight that MSC transplantation is potentially a novel therapeutic strategy for severe KD due to their anti-inflammatory and immunoregulatory functions.

10.6 Polyarteritis Nodosa (PAN)

Polyarteritis nodosa (PAN) is characterized by necrotizing vasculitis in medium- or small-sized arteries or angiographic abnormalities. Patients may also have other symptoms of the skin, muscle, kidneys, gastrointestinal tract, and heart. Treatment of severe PAN includes corticosteroids, cyclophosphamide, and mycophenolate mofetil. Despite therapy, mortality remains high. Biologic agents including rituximab were also described for children with systemic PAN.

Similar to other autoimmune disorders, intense immunosuppression followed by reconstitution of immune system with a stem cell transplant has been proposed as a last-ditch treatment. A 22-year-old Caucasian female with an 8-year history of juvenile-onset PAN was treated with autologous peripheral blood stem cell transplantation [24]. Over the following 8 years, she had multiple flares of disease which

could not be controlled by oral and i.v. corticosteroids, cyclophosphamide (to a total dose of 51 g), oral colchicine, IVIG, and plasmapheresis. In the 18 months before autologous HSCT, she suffered increasingly frequent flares and repeat angiography showed new aneurysms in the hepatic arteries. She was therefore offered autologous HSCT. After administration of cyclophosphamide (1.5 g/m^2), stem cells were harvested by leucopheresis after stem cell mobilization with granulocyte-colony stimulating factor from the bone marrow. CD34$^+$ cells were purified by magnetic bead selection. Immunosuppressive conditioning regimen was compromised of 20 mg CAMPATH-1H (days −9 to −5), fludarabine 30 mg/m2 (days −8 to −4), and cyclophosphamide 1 g/m^2 on days −3 and − 2. After HSCT she remained well and discontinued immunosuppressive medication other than low-dose prednisolone (<10 mg/day) for the next 5 months. Unfortunately she developed a new vasculitic rash on the lower extremities that were not present before HSCT over the ensuing year. Fourteen months after HSCT, she developed autoimmune hyperthyroidism. In addition she was positive for thyroglobulin antibodies and p-ANCA. At 18 months, the patient developed autoimmune thrombocytopenia. The platelet count recovered with IVIG and oral steroids. By sequence-specific T-cell receptor (TCR) heteroduplex (HD) analysis of purified T-cell subsets, the researchers showed that clonal T-cell expansions, present within 2 months of HSCT when the majority of the T cells express CD45RO$^+$, were subsequently within the CD45RA$^+$ T-cell subset at 1 year after HSCT. These data suggested that T cells underwent reversion from CD45RO$^+$ to RA$^+$. Thus in patients who may have a genetic background which predisposes them to autoimmunity, immune reconstitution after HSCT can be associated with new autoimmune phenomena [19].

10.7 Takayasu Arteritis

Takayasu arteritis (TA) is the large vessel vasculitis (LVV). The clinical diagnosis of TA is usually challenging. Due to the non-specific symptoms and the absence of specific laboratory parameters, TA is often unrecognized in the acute early phase. There have been few evidence-based therapies for TA. The general therapeutic approach is induction of remission (high dose corticosteroid combined with another immunosuppressant), followed by maintenance therapy (lower dose corticosteroid combined with a maintenance immunosuppressive agent, usually methotrexate). About half of patients respond to steroids and the non-responders may benefit from other forms of immunosuppression [25]. In addition, methotrexate, azathioprine, mycophenolate mofetil, leflunomide, chlorambucil, antimalarials, and cyclophosphamide have been used in children as first- or second-line agents. Biologic therapies, including anti-TNFα mAb and tocilizumab (a monoclonal antibody against interleukin 6 receptor), were reported to be effective [26, 27].

Autologous HSCT for TA was reported in a Brazilian woman [28]. She was diagnosed in June 1990 when she was 41 years old. The arteriography showed irregularities and stenosis of the abdominal aorta. The patient was treated with various immunosuppressive agents, such as steroids, oral cyclophosphamide,

mycophenolate mofetil, methotrexate, and chlorambucil, but all of those therapies failed. In October 2002, a magnetic resonance angiogram showed narrowing and irregularities in both carotid and subclavian arteries and in the brachiocephalic artery. The worsening of clinical symptoms prompted the patient and her physician to choose experimental autologous HSCT in April 2003. Hematopoietic stem cells were mobilized with cyclophosphamide (2 g/m^2) and granulocyte colony-stimulating factor. Conditioning regimen included cyclophosphamide (50 mg/kg/day × 4) plus rabbit anti-thymocyte globulin. After transplantation the clinical condition improved rapidly; there was complete resolution of headache, dizziness, and malaise, while limb claudication was significantly reduced. Sixty days after HSCT, magnetic resonance angiography showed correction of the stenosis of the brachiocephalic artery and reduction in the irregularities of the left carotid artery and of the left subclavian artery. On day 320, arterial pulses of the left lower limbs and of the carotid arteries showed normal shape and speed by Doppler US, and the wave speed of abdominal aorta increased to 73 cm/s. In this case the surprisingly fast improvement in artery structure and function is unexpected and deserve further studies.

10.8 DADA2

Deficiency of adenosine deaminase type 2 (DADA2) is an autosomal recessive disease resembling polyarteritis nodosa and is caused by mutations in the *CECR1* gene [29, 30]. The principal clinical features include livedo racemosa, vasculitic peripheral neuropathy, digital ischemia, and cutaneous ulceration. Anti-TNF-alpha mAb is particularly efficacious for this form of monogenic vasculitis [31].

Allogeneic HSCT has been reported to be successful in a DADA2 patient [32]. Two brothers with ADA2 deficiency had a homozygous mutation in *CECR1* (p.R169Q). One brother presented in 1999, at 6 months of age. He underwent HSCT in 2003 from a matched unrelated donor after myeloablative conditioning. The patient showed rapid immune reconstitution, with resolution of cytopenias, skin lesions, hepatosplenomegaly and hypercoagulability, and recovery of serum ADA2 levels to the normal range for his age. MRI revealed the brain was negative for vasculopathic changes. The absence of vasculopathy and the resolution of hypercoagulability after HSCT suggests that the correction of ADA2 blood levels reduces macrophage activation and endothelial disruption, both of which probably contribute to vasculitis. This patient's younger brother presented in 2009 at 6 years of age. Treatment with an anti-TNF alpha mAb (etanercept) stabilized his clinical condition, although he has persisting profound lymphopenia and low-grade inflammation.

Patients with DADA2 demonstrate skewed macrophage development toward the M1 pro-inflammatory phenotype as opposed to the M2 anti-inflammatory phenotype. M1 macrophages are known to produce TNF alpha, which could explain why anti-TNF alpha mAb seems particularly effective in DADA2. Due to the fact that MSC may skew macrophage from M1 to M2 phenotype, we hypothesize that MSC may be beneficial for DADA2 patients. Future clinical trials are needed to support our hypothesis.

10.9 CANDLE and SAVI

CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) syndrome is a recessive disease caused by gene mutations in the proteasome pathway and is classified as a proteasome-associated autoinflammatory syndrome (PRAAS). Mutations in *PSMB8*, *PSMB4*, *PSMB9*, *PSMA3*, and *POMP* are proposed to be responsible for CANDLE syndrome. Effective treatments for CANDLE syndrome are still elusive. Oral corticosteroids, methotrexate, cyclosporine, azathioprine, or intravenous immunoglobulins have achieved some improvements. CANDLE is associated with dysregulated type I interferon production; therefore targeting this pathway with selective JAK1/2 kinase inhibitor baricitinib has been proposed and a treatment protocol has been started.

Stimulator of interferon genes (STING)-associated vasculitis of infancy (SAVI) arises from sporadic/dominant mutation in the *TMEM173* gene and presents early in life with a vasculitic rash affecting the cheeks, nose, and peripheries. Standard vasculitis therapies are ineffective. Cutaneous vasculitis and deteriorating lung function usually continue relentlessly throughout childhood, with development of pulmonary hypertension and lung fibrosis, often with fatal outcome. Reports again suggest that early treatment targeting the interferon pathway (e.g., with JAK inhibitors) may offers some benefits to the patients.

Although no clinical trials have been reported for CANDLE and SAVI with either MSCs or HSCT, we consider that both strategies may be helpful in alleviating the patients' symptoms and improve their quality of life.

10.10 Conclusion

Considerable therapeutic advances for the treatment of vasculitis have been made in the past 10 years, including application of MSCs and HSCT. As new treatments that facilitate corticosteroid sparing are emergently needed, robust randomized controlled trials are expected to confirm the preliminary results of MSCs and HSCT. However it is a great challenge to enroll enough patients for randomized controlled trials aiming the rare diseases. Thus international cooperation is necessary in the future.

References

1. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised international Chapel Hill consensus conference nomenclature of Vasculitides. Arthritis Rheum. 2013;65(1):1–11.
2. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. N Engl J Med. 1999;341(17):1284–91.
3. Barron KS, Shulman ST, Rowley A, et al. Report of the National Institutes of Health workshop on Kawasaki disease. J Rheumatol. 1999;26(1):170–90.

4. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med. 1992;116(6):488–98.
5. Scott DG, Watts RA. Systemic vasculitis: epidemiology, classification and environmental factors. Ann Rheum Dis. 2000;59(3):161–3.
6. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;8(2):315–7.
7. Figueroa FE, Carrión F, Villanueva S, Khoury M. Mesenchymal stem cell treatment for autoimmune diseases: a critical review. Biol Res. 2012;45(3):269–77.
8. Zhao RC, Liao L, Han Q. Mechanisms of and perspectives on the mesenchymal stem cell in immunotherapy. J Lab Clin Med. 2004;143(5):284–91.
9. Klinker MW, Wei CH. Mesenchymal stem cells in the treatment of inflammatory and autoimmune diseases in experimental animal models. World J Stem Cells. 2015;7(3):556–67.
10. Lee HK, Lim SH, Chung IS, et al. Preclinical efficacy and mechanisms of mesenchymal stem cells in animal models of autoimmune diseases. Immune Netw. 2014;14(2):81–8.
11. Rad F, Ghorbani M, Mohammadi Roushandeh A, Habibi Roudkenar M. Mesenchymal stem cell-based therapy for autoimmune diseases: emerging roles of extracellular vesicles. Mol Biol Rep. 2019;46(1):1533–49.
12. Jantunen E, Myllykangas-Luosujärvi R. Stem cell transplantation for treatment of severe autoimmune diseases: current status and future perspectives. Bone Marrow Transplant. 2000;25(4):351–6.
13. Gardner-Medwin JM, Dolezalova P, Cummins C, Southwood TR. Incidence of Henoch-Schonlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. Lancet. 2002;360(9341):1197–202.
14. Ozen S. The spectrum of vasculitis in children. Best Pract Res Clin Rheumatol. 2002;16(3):411–25.
15. Chartapisak W, Opastiraku S, Willis NS, Craig JC, Hodson EM. Prevention and treatment of renal disease in Henoch-Schonlein purpura: a systematic review. Arch Dis Child. 2009;94(1):132–7.
16. Mu K, Zhang J, Gu Y, et al. Cord-derived mesenchymal stem cells therapy for liver cirrhosis in children with refractory Henoch-Schonlein purpura: a case report. Medicine (Baltimore). 2018;97(47):e13287.
17. Tsukamoto H, Nagafuji K, Horiuchi T, et al. A phase I-II trial of autologous peripheral blood stem cell transplantation in the treatment of refractory autoimmune disease. Ann Rheum Dis. 2006;65(4):508–14.
18. Tyndall A, Passweg J, Gratwohl A. Haemopoietic stem cell transplantation in the treatment of severe autoimmune diseases 2000. Ann Rheum Dis. 2001;60(7):702–7.
19. Ashihara E, Shimazaki C, Hirata T, et al. Autoimmune thrombocytopenia following peripheral blood stem cell autografting. Bone Marrow Transplant. 1993;12(3):297–9.
20. Mccrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association[J]. Circulation. 2017;135(17):e927–99.
21. Eleftheriou D, Levin M, Shingadia D, Tulloh R, Klein NJ, Brogan PA. Management of Kawasaki disease. Arch Dis Child. 2014;99(1):74–83.
22. Noguchi S, Saito J, Kudo T, et al. Safety and efficacy of plasma exchange therapy for Kawasaki disease in children in intensive care unit: case series. JA Clin Rep. 2018;4(1):25.
23. Uchimura R, Ueda T, Fukazawa R, et al. Adipose tissue-derived stem cells suppress coronary arteritis of Kawasaki disease in vivo. Pediatr Int. 2019; https://doi.org/10.1111/ped.14062.
24. Wedderburn LR, Jeffery R, White H, et al. Autologous stem cell transplantation for paediatric-onset polyarteritis nodosa: changes in autoimmune phenotype in the context of reduced diversity of the T- and B-cell repertoires, and evidence for reversion from the CD45RO(+) to RA(+) phenotype. Rheumatology (Oxford). 2001;40(11):1299–307.
25. Maffei S, Renzo MD, Bova G, et al. Takayasu's arteritis: a review of the literature. Intern Emerg Med. 2006;1(2):105–12.

26. Tanaka F, Kawakami A, Iwanaga N, et al. Infliximab is effective for Takayasu arteritis refractory to glucocorticoid and methotrexate. Intern Med. 2006;45(2):313–6.
27. Nakaoka Y, Higuchi K, Arita Y, et al. Tocilizumab for the treatment of patients with refractory takayasu arteritis. Int Heart J. 2013;54(2):405–11.
28. Voltarelli JC, Oliveira MC, Stracieri AB, et al. Haematopoietic stem cell transplantation for refractory Takayasu's arteritis. Rheumatology (Oxford). 2004;43(10):1308–9.
29. Zhou Q, Yang D, Ombrello AK, et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. N Engl J Med. 2014;370:911–20.
30. Navon Elkan P, Pierce SB, Segel R, et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. N Engl J Med. 2014;370(9):921–31.
31. Nanthapisal S, Murphy C, Omoyinmi E, et al. Deficiency of adenosine deaminase type 2 (DADA2): a description of phenotype and genotype in 15 cases. Arthritis Rheumatol. 2016;68(9):2314–2.
32. Van Montfrans J, Zavialov A, Zhou Q. Mutant ADA2 in vasculopathies. N Engl J Med. 2014;371(5):478–9.