Thromboangiitis Obliterans

Ahmet Rüçhan Akar, MD, FRCS (CTh)^{*}

M. Bahadır İnan, MD

Çağdaş Baran, MD

Address

^{*}Department of Cardiovascular Surgery, Heart Center, Cebeci Hospitals of Ankara
University School of Medicine, Dikimevi, Ankara, Turkey
Email: akarruchan@gmail.com

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Opinion statement

Ischemia in TAO involves the upper and lower extremities, caused by infrapopliteal or infrabrachial vaso-occlusive disease. Features of advanced TAO include ischemic ulcerations and digital gangrene. Tobacco is strongly associated with the pathogenesis and progression of TAO, and results in a high degree of social, and financial costs, in addition to chronic morbidity. Smoking cessation is the only fully effective therapy for TAO. Counseling, analgesia, and local wound care are essential components to the management of patients with ischemic ulcers. Reported evidence indicates that intravenous iloprost is an effective pharmacological treatment option for patients with critical limb ischemia (CLI), and may also help heal ulcers and relieve rest pain in patients with TAO. Distal surgical revascularization may obviate amputations and improve quality of life. Emerging research supports a role for endothelin receptor antagonists, immunoadsorption, growth factors, gene and stem cell-based therapies for the treatment of patients with TAO and CLI.

Introduction

In 1879, Felix von Winiwarter described a 57-year-old man with a prolonged history of foot pain that eventually progressed to gangrene and limb loss, which is now recognized as the first published case of a patient with critical limb ischemia (CLI) [1, 2••, 3]. In 1908, Leo Buerger described a new and unusual form of progressive vaso-occlusion in Polish and Russian immigrants who underwent amputation for CLI [4]. Based on his findings, Buerger called the disease “thromboangiitis obliterans” to distinguish it from arteriosclerosis obliterans (ASO). In 1898, Haga

reported similar clinical features resulting in spontaneous gangrene [5]. Allen and Brown reviewed 200 patients diagnosed with TAO who were evaluated at the Mayo clinic between 1922 and 1926 [6]. However, between the 1930s and 1960s, numerous investigators expressed skepticism concerning the identity of TAO [7–9]. In the early 1960s, several authorities considered TAO a distinct diagnosis that should be separated from ASO [10–14]. Today, TAO is accepted as a vasculopathy *sui generis* with a distinct presentation and histopathology [2••, 15–19].

TAO most commonly affects patients from the Middle East, Asia, the Mediterranean, and Eastern Europe. The incidence varies by geographic location [2••, 20–23]. Estimated worldwide prevalence is 5 to 12 per 100,000 population per year, ranging from 0.25 to 693 per 100,000 population per year. In 1947, the prevalence of Buerger's disease was 104 per 100,000 patient registrations; in 1986, that number had dropped to 12.6 per 100,000 patient registrations [16, 24]. The overall prevalence of TAO ranges from approximately 5 cases per 100,000 persons among the Japanese to more than 10 per 100,000 persons in the Middle East, Asia, Mediterranean, and Eastern European countries. In Latin America and Africa, TAO is rarely reported [25]. Worldwide, Buerger's disease accounts for a substantial amount of peripheral vascular disease: 66 % in Korea, and 45 to 63 % in India [2••], 0.75 % in North America, 0.5 to 5.6 % in Western Europe [20, 26–29], 3 to 39 % in Eastern Europe and the Mediterranean [23, 28, 30], 80 % in Israel among Ashkenazi Jews [31], and 16 % in Japan [32–34].

The etiology of Buerger's disease is unknown [2••, 16, 22, 35, 36]. However, the close association between disease activity and use of tobacco in any form is beyond debate. Genetic predisposition, immune-mediated mechanisms, hypercoagulable states, and an oral infection-inflammatory pathway [37] have been implicated as potential etiologic factors. However, the role of thrombotic risk factors including factor V Leiden and prothrombin 20210G/A mutations, hyperhomocysteinemia, and platelet aggregation responses in patients with TAO remains controversial [38–47].

Buerger's disease is characterized by segmental inflammatory cell infiltration of the vessel wall and arterial or venous thrombotic occlusions [48, 49]. Hypercellular thrombus formation and preserved architecture of vessel walls is well established in TAO [50••]. Earlier studies suggested TAO as a thrombotic disorder complicated by vasculitis, namely transmural neutrophilic infiltration [32, 51]. Today, there are compelling reasons to believe that the primary event is the activation of antigen-presenting cells following endothelial cell damage induced by an unidentified antigen, possibly tobacco glycoproteins [49, 50••, 52, 53]. Cellular and humoral inflammation, which leads to thrombotic occlusion of the blood vessels, is restricted to the intima of the artery, which defines TAO as an endarteritis [49, 52]. Intimal inflammation followed by T cell infiltrations might result in early arterial occlusion, which is the pathomnemonic finding in TAO [54]. Regardless of

the pathologic stage, the internal elastic lamina and the architecture of the vascular walls are well preserved in TAO, in contrast with atherosclerosis and systemic vasculitis [2••, 49, 50••, 51, 55, 56]. Inflammatory cell infiltration is found in the intimal layer and the thrombus [49, 57].

The evolution of TAO is often categorized into three stages [51]. In the acute phase, inflammation affecting the small-caliber and medium-caliber (1- to 5-mm diameter) arteries and veins is observed. The primary features of TAO during the acute phase include an occlusive, highly cellular arterial thrombus, polymorphonuclear cell infiltrate with leukocytoclasia, giant cells, and microabscess formation; marked inflammation of the entire vessel wall and neurovascular bundle [11, 24, 55]. However, most of the infiltrating cells are detected in the intima [52]. The intense inflammatory infiltration and cellular proliferation seen in acute lesions are distinctive, especially when veins are involved. Multinucleated giant cells can be seen, but fibrinoid necrosis and granuloma are not observed [49]. During the intermediate or subacute phase, there is progressive organization of the occlusive thrombus, with partial recanalization and disappearance of the microabscesses [49]. An inflammatory response, including CD3+ pan-T cells, CD4+ T helper-inducer cells, and CD20+ pan-B cells, against the internal elastic lamina of the affected vessels has been shown in detail [49, 54, 57]. In addition, CD68+ macrophages or S-100+ dendritic cells are found in the intima during both the acute and subacute stages [52]. IgG, IgM, and IgA and complement factors 3d and 4c are deposited along the inner aspect of the internal elastic lamina [49]. The chronic phase or end-stage lesion is characterized by thrombus organization followed by recanalization, prominent vascularization of the media, and perivascular fibrosis [51, 55]. Regardless of the pathologic stage, the internal elastic lamina and the architecture of the vascular walls are well preserved in TAO, in contrast with atherosclerosis and other types of systemic vasculitis [2••, 49, 51, 55, 56].

TAO usually presents in patients younger than 50 years old [18, 58]. The median age at diagnosis is 34 years [17]. The disease starts distally, but then moves to involve more proximal arteries [55]. The most common symptoms are claudication affecting the arch or lower calf due to infra-popliteal occlusive disease [55]. Foot claudication is particularly characteristic [59]. Claudication limited to the calf may occur, but this is unusual because the disease does

not commonly progress proximally to involve either the popliteal artery above the knee or the superficial femoral artery. Foot and arch claudication may be misattributed to orthopedic problems. Early symptoms may also include cold insensitivity, burning pain in the feet and hands, dependent rubor [60], cyanosis, skin atrophy, migratory superficial thrombophlebitis [61], Raynaud's phenomenon [25, 62–64], and reduced hair growth [65]. Rarely, TAO has been associated with visceral [66–86], cerebral [87–91], coronary [92–101] internal thoracic artery [94, 95], and multi-organ involvement [102, 103].

The major aims of diagnostic evaluations are to exclude ASO, thromboembolism, and other vasculitides. Pulse volume recordings and four-limb segmental arterial pressure measurements are usually normal above the knee, but markedly reduced distally [36]. Abnormal digital plethysmographic patterns in both lower and upper extremities may objectively document distal occlusive disease in a patient meeting the clinical criteria for TAO [17, 27, 35, 104, 105]. Arterial duplex scanning may be used to evaluate the patient for atherosclerotic lesions. Furthermore, the corkscrew collaterals may be identified using continuous wave Doppler ultrasound, which demonstrates a monophasic (rather than triphasic) waveform, with forward flow occurring during both systole and diastole. When the difference in flow between systole and diastole has an amplitude >3 mm, the Doppler signal produced by the collateral artery takes on a characteristic undulating appearance (the “snake sign”). When the amplitude is <3 mm, the Doppler signal takes on the appearance of a row of dots along the blood vessel's path (the “dot sign”) [106, 107]. Transcutaneous oxygen pressure can be used to confirm the ankle-toe gradient and the severity of ischemia.

Emboli as a cause of distal ischemia should be ruled out, as the signs and symptoms of embolic occlusions can mimic those of TAO. Cardiac investigations, including electrocardiography, rhythm monitoring, and echocardiography, are recommended to rule out cardiac and thoracic aortic sources of emboli to the involved extremity. Ultrasound may be used to rule out a proximal source of emboli from an abdominal aortic aneurysm or atherosclerotic aorta. Furthermore, ischemic ulcerations with evidence of secondary infection should be evaluated using imaging studies such as magnetic resonance to look for evidence of osteomyelitis [108]. Digital subtraction

angiography (DSA) plays an important role in both establishing the diagnosis of TAO and ruling out other causes of ischemia. Arteriographic findings are not diagnostic of TAO. Normal proximal arteries, without evidence of atherosclerotic disease, followed by gradually increasing involvement, most severe in the digits, and characterized by segmental occlusion alternating with normal-appearing arteries [27], and collateralization with corkscrew-shaped collaterals (Martonell's sign, also described as “tree root” or “spider's leg” collaterals) are the common features of TAO [109, 110]. The infrapopliteal or infrabrachial arteries are the most common sites of occlusion. Small corkscrew patterns are associated with a higher prevalence of ischemic ulcers compared to large corkscrew collaterals [111]. Although corkscrew collaterals, which represent a widened vasa vasorum, suggest TAO to many physicians [109], this finding is not pathognomonic. Corkscrew collaterals can be seen in a wide variety of rheumatic diseases such as scleroderma, CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal disease, sclerodactyly, telangiectasia), systemic lupus erythematosus (SLE), rheumatoid vasculitis, and the antiphospholipid-antibody syndrome [2••]. Furthermore, cocaine, amphetamine, and cannabis can mimic Buerger's disease [112–118]. Gadolinium-enhanced magnetic resonance angiography (MRA) and 64-slice multidetector computed tomographic angiography may also be useful to detect segmental occlusions or corkscrew collaterals; they may also be useful to search for a proximal source of emboli or to exclude other forms of systemic vasculitis [110].

A century after its first description, the major clinical challenge in TAO is the absence of universally accepted diagnostic criteria [2••, 15, 119–121]. The traditional diagnosis of TAO is based on Shionoya's criteria, which requires all five elements: (1) smoking history, (2) onset before age 50, (3) infrapopliteal arterial occlusive lesions, (4) either upper limb involvement or phlebitis migrans, and (5) an absence of atherosclerotic risk factors other than smoking [15]. In 1992, Papa and Adar proposed various clinical, angiographic, histopathologic, and exclusionary criteria, and in a second report they proposed a point-based scoring system to improve the diagnostic certainty [122]. More stringent major and minor supportive criteria were developed by Mills and Porter, based on a cohort of patients in Oregon [123]. All investigators accepted the exclusion of atherosclerotic

risk factors other than smoking. Therefore, TAO is a clinical diagnosis, and the diagnosis requires investigations aimed at excluding other possible diagnoses. A biopsy is rarely needed unless the patient presents with atypical features, such as large-artery involvement or age older than 45 years [2••]. Kroger suggested that the possibility of arteriosclerosis should be discounted only in young patients, aged 20 to 30 years [121].

There are no specific tests to diagnose TAO; however, serologic testing for autoantibodies, thrombophilia, and other forms of systemic vasculitis should be included in the screening process. Acute phase reactants, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are typically normal or slightly elevated, unless there is extensive involvement of the extremities. The absence of immunological markers—including abnormal complement levels, rheumatoid factor, antinuclear antibodies, anticentromere antibodies, anti-SCL-70 antibodies, ANCA, and cryoglobulins—is characteristic of TAO.

The initial evaluation includes a history and physical examination; this is followed by a combination of laboratory tests that may include markers of inflammation, immunoactivation, and coagulation. TAO involvement of the infrapopliteal arteries in the lower extremities and infrabrachial arteries in the upper extremities distinguishes it from ASO. TAO differs from most other types of vasculitis in that the usual serologic markers (elevated acute phase reactants such as ESR and CRP, presence of circulating immune complexes, and presence of autoantibodies such as antinuclear antibody, rheumatoid factor, and complement levels) are normal or negative [55]. If ASO or other forms of systemic vasculitis cannot be

excluded based on clinical findings and noninvasive testing, the patient should undergo diagnostic digital subtraction angiography or magnetic resonance angiography. Recently, 18F-fluorodeoxyglucose positron emission tomography has been investigated in TAO case series but found to be unsuitable investigative procedure for the diagnosis of TAO [124].

The diagnosis can be confirmed by biopsy of a subcutaneous nodule or involved vein, which may show the characteristic acute phase lesion [55, 118]. TAO has important features that are distinguishable from other forms of vasculitis [125], including a highly inflammatory thrombus with relative sparing of the blood vessel wall; normal levels of acute phase reactants; and absent immunoactivation markers. TAO also has a unique immunophenotype that differs from ASO and thromboembolism, including a segmental inflammatory process in the vessel wall, progressive organization of a highly inflammatory thrombus in the vessel lumen, and an inflammatory response to the intact internal elastic lamina of the affected vessels [49, 57]. Preservation of the internal elastic lamina distinguishes TAO from the true necrotizing forms of arteritis [49, 126, 127].

Significantly lower survival rates were observed among the TAO patients than in the matched US population, the average age at death was 52.2 ± 8.9 years [128]. Ohta and colleagues reported that cumulative survival rates were 97.0 % at 5 years, 94.4 % at 10 years, 92.4 % at 20 years, and 83.8 % at 25 years (mean follow-up, 10.6 years) in patients with Buerger's disease [129]. In this series, necrotic lesions rarely occurred or reoccurred in patients older than 60 years [129].

Treatment

The mainstays of treatment for TAO include smoking cessation, daily foot and hand hygiene, an exercise program, pain relief (if warranted), additional pharmacologic treatment in patients with CLI, limited debridement and appropriate antibiotics for ischemic ulcers, and revascularization (if feasible).

Lifestyle, diet, and smoking cessation

Counseling and management following the diagnosis of TAO are dominated by the cessation of smoking in any form [17, 55, 125, 130], including passive smoking [131]. The hazards of continued smoking in patients with TAO seems to be independent of factors such as the number of cigarettes smoked per day

[125]; whether the tobacco product is in the form of cigarettes, bidis, cigars, chewing tobacco, or snuff [132–134]; cigarette characteristics; and smoking behavior, including degree of inhalation. Strategies to stop tobacco use, smoking-cessation programs, pharmacotherapy using bupropion or varenicline, and exercise training form the cornerstone of treatment [135]. Nicotine replacement therapy may result in disease progression, thus should be avoided [2••, 65]. However, in terms of limb salvage in a stage of CLI in patients with TAO, smoking cessation may not be sufficient. Daily foot and hand hygiene as well as avoidance of trauma, vibration, and cold are easily applied measures to prevent ischemic ulcers. Any injury to the involved extremity should be treated promptly.

Analgesia

Analgesia is often required in patients with rest pain and ischemic ulcers. Opioids, nonsteroidal anti-inflammatory drugs, antidepressants, and neuronal block may relieve symptoms.

Regional sympathetic blockade

Guanethidine, an adrenergic neuron blocker that inhibits the presynaptic release and subsequent reuptake of noradrenaline from postganglionic sympathetic nerve endings, has been proposed for the treatment of TAO [136–139]. Intravenous regional sympathetic blockade with guanethidine has been described by Hannington-Kiff [140]. This “chemical sympathectomy” is based on multiple sessions of intravenous regional sympathetic blockade with lidocaine and guanethidine using Bier’s arterial arrest [141, 142]. However, despite promising case reports in patients with ischemic rest pain and non-healing ulcerations, limitations regarding the use of this therapy still exist [136].

Spinal cord stimulation

There are increasing reports in the literature regarding the use of implantable spinal cord stimulators in patients with TAO [143–148]. Electrical spinal cord stimulation relieves pain through several mechanisms, including preventing transmission of painful stimuli through the corresponding dermatomes, stimulation of the production of inhibitory neurotransmitters in the spinal cord, and inhibition of sympathetic vasoconstriction with consequent improvement in peripheral microcirculation [143, 146, 148]. Spinal cord stimulation successfully addresses the neurogenic, but not the somatic, aspects of pain in patients with TAO [139]. Spinal cord stimulation can be attempted when other forms of therapy are ineffective [125].

Wound management

Negative-pressure wound therapy may have role in the treatment debilitating complex chronic ulcers in patients with TAO [149–151]. Given the lack of supportive data, hyperbaric oxygen therapy should be considered only in patients with ischemic ulcers, osteomyelitis, or necrotizing fasciitis who are refractory to other forms of treatment [112, 152–158]. Daily arterial flow pump

therapy [159] or intermittent pneumatic compression pump [160] may relieve symptoms when cessation of smoking is achieved.

Pharmacologic treatment

Treatment must be tailored to the individual and is often based on the patient's clinical presentation. TAO has conventionally been treated with antiplatelet agents including clopidogrel, oral anticoagulants, dextran, pentoxifylline, cilostazol, phenylbutazone, pyridinolcarbamate, inositol niacinate, calcium channel blockers, and nonsteroidal anti-inflammatory agents. Immunosuppressive drugs, such as cyclophosphamide and corticosteroids, do not have a widely recognized role in the treatment of TAO, and no randomized controlled trials have been reported assessing the efficacy of any of these agents. In the setting of continued smoking, no medication has proved uniformly successful. Appropriate antibiotics and nonsteroidal anti-inflammatory agents should be used in patients with complicated phlebitis, cellulitis, or osteomyelitis.

Iloprost Infusion

Moderate quality of evidence exists with limited number of randomized trials in pharmacological treatment of Buerger's disease with critical limb ischemia [161••]. In a European multicenter randomized, double-blinded trial involving patients with TAO and critical limb ischemia, Fiessinger and Schafer compared 6-h infusion of iloprost (0.5 to 2.0 ng/kg/min) and oral aspirin (100 mg/day) for a 28-day trial period [162]. Among 152 patients, 133 patients fulfilled the entry criteria of rest pain, ischemic ulceration, or gangrene [162]. At 28 days of treatment, iloprost was superior to aspirin at achieving ulcer healing or relief of ischemic pain; 85 % of patients in the iloprost group improved versus 17 % in the aspirin group. Furthermore, at 6 months, the response rate was 45 of 51 (88 %) patients treated with iloprost, compared with 12 of 44 (21 %) patients treated with aspirin. Only 6 % of patients in the iloprost group ultimately required amputation, compared with 18 % in the aspirin group [162]. Pharmacological treatment should be considered in patients with rest pain and ischemic ulcers [161••].

Oral iloprost

The European TAO Study Group conducted a double blinded, randomized, placebo-controlled trial comparing oral iloprost (100 or 200 mcg) with placebo for 8 weeks among 319 patients with ischemic rest pain or ulcerations recruited from 22 centers in six countries in Europe [163]. Duration of treatment was 6 weeks. The primary endpoint was total healing of the most important lesion, and the secondary endpoint was total relief of pain at rest without the need for analgesics at 6 months. The combined endpoint consisted of the patient's being alive with no major amputation, no lesions, no rest pain, and no analgesic use. After 6 months of therapy, low-dose iloprost was significantly better than placebo at relieving rest pain without the use of analgesics, and for achieving the combined endpoint [163]. However, neither dose of oral iloprost showed a significant effect on the total healing of lesions compared with placebo.

Cilostazol

In one small study, cilostazol, a phosphodiesterase type III inhibitor with vasodilator and mild antiplatelet properties, was effective at improving ischemic ulcerations in patients with refractory digital ischemia [127]. The role of cilostazol in TAO is, however, still not clear.

Endothelin receptor antagonists

Bosentan, an oral dual endothelin-1 receptor antagonist targeting two transmembrane receptors namely ETA and ETB, has been useful in patients with TAO and ischemic lesions [164–166]. Bosentan has selective vasodilatory, anti-inflammatory, and antifibrotic properties. Previous case series showed clinical and angiographic improvement in 10 out of 12 patients with ulcers and/or pain at rest [167]. De Haro et al. reported that bosentan therapy (125 mg/12 h) maintained for 4 months resulted in clinical improvement and complete healing of the ulcers in a single-center prospective study with 48 months follow-up data in patients with TAO and ischemic ulcers unresponsive to conventional therapies [168]. Only 2 out of 22 extremities (9 %) underwent major amputation. Well-conducted randomized clinical trials are, however, still needed, especially in patients with pain at rest and ischemic ulcers.

Surgery

Lumbar or thoracic sympathectomy

In a randomized, multicenter study, the Turkish Buerger's Disease Research Group compared the results of lumbar sympathectomy ($n=78$) to 28 days of intravenous iloprost ($n=84$) in 162 patients with critical limb ischemia and TAO [169]. The primary endpoint of the study was complete healing without major amputations or pain at 4 and 24 weeks. Complete healing was achieved in 61.9 % of the iloprost group and 41 % of the lumbar sympathectomy group at 4 weeks ($P=.012$) and in 85.3 versus 52.3 %, respectively, at 24 weeks ($P<.001$) [169]. Kothari et al. recently reported that thoracoscopic dorsal sympathectomy reduces pain in patients with upper limb involvement in a recent case series of 25 TAO patients from India [170].

Distal revascularization

The role of revascularization in TAO is not clear. Revascularization is often not feasible because of the distribution of diffuse, segmental arterial involvement and the distal nature of the disease [55]. Distal arterial spasm during dissection and poor-quality veins owing to phlebitis are other disease-specific handicaps. The arterial circulation of the lower extremity generally cannot serve as the distal anastomotic site for bypass surgery, resulting in suboptimal patency rates. However, if the patient has critical limb ischemia and a distal target vessel is present, bypass surgery using autologous vein should be considered [171, 172]. Furthermore, arterial bypass of the larger vessels may be used in selected cases. In 1974, Inada and associates demonstrated that of their 236 patients with Buerger's disease, only 11 (4.6 %) had lesions that were amenable to surgical

revascularization [173], whereas a vasculitis database from Japan revealed that 15.5 % of TAO patients underwent surgical revascularization [174]. Dilege and associates reported that 36 of their 94 patients with TAO (38.3 %) were deemed eligible for revascularization, but only 27 patients (28.7 %) actually underwent revascularization procedures [175]. In this study, any crural vessel with at least 10 cm of patency, preferably in continuation with the pedal arch or draining with a good collateral network, was considered appropriate for revascularization. The patency rates at 12, 24, and 36 months were 59.2, 48, and 33.3 %, respectively. The limb salvage rate was, however, 92.5 %. Bypass surgery was most frequently required below the trifurcation segment of the knee joint, with a cumulative patency rate of 54.6 % at 5 years [176]. In a retrospective review of 216 patients with TAO over a 10-year period, Sayin and colleagues reported that lumbar sympathectomy was performed in 85 % and thoracic sympathectomy in 9.3 % of TAO patients [177]. Twenty-one patients (9.7 %) underwent direct arterial reconstruction of varying types. The investigators noted that four of the five endarterectomized segments had occluded by the 7-year follow-up [177]. Another study from Japan showed that a strategy of aggressive distal bypass surgery using autologous disease-free vein grafts for TAO may provide acceptable primary and secondary patency rates [171]. In this series of 71 autogenous vein bypasses in 61 patients with TAO, indications for surgery included the following: claudication (41 %) and gangrene or ischemic ulcer (59 %). The patency rates in the postoperative nonsmoking group were significantly higher than in the smoking group (66.8 versus 34.7 %; $P < .05$) [171]. Predictors of early graft failure were poor quality vein, inadequate technique for anastomosis, inadequate tunneling, anastomosis to a diseased artery, arterial spasm, and vein graft intimal hyperplasia [171]. Late failures were due to disease progression, especially in smokers, vein graft intimal hyperplasia or aneurysm, atherosclerosis, and competition with collateral flow [171]. Bozkurt and colleagues reported cumulative secondary patency rates of 57.9 % for bypass grafts at a mean follow-up of 5.4 years in 19 patients with Buerger's disease [30]. Cumulative patency was 70 % (7 of 10) for saphenous vein grafts, 50 % (3 of 6) for polytetrafluoroethylene grafts, and 33.3 % (1 of 3) for composite grafts. Different distal bypass techniques and routes have been described to obtain better anatomical orientation and patency rates in patients with TAO [178–180]. Successful local flap transfers after distal bypass surgery have been reported in selected cases [181–184].

Distal venous arterialization may be offered as a last surgical resort for limb salvage in the absence of graftable distal arteries [185–189]. Distal venous arterialization can successfully salvage the critically ischaemic lower limb with few serious complications. A recent meta-analysis showed that overall 1-year foot preservation was 71 % (95 % CI, 64–77 %) and 1-year secondary patency was 46 % (95 % CI, 39–53 %) after distal venous arterialization [186].

Interventional procedures

Immunoadsorption

Recent pilot studies demonstrated near complete pain relief, increased maximum walking distance, and tissue perfusion after selective removal of

circulating immunoglobulins and antibodies from patient's plasma using immunoabsorption techniques [190, 191]. In one study, agonistic autoantibodies directed against G-protein coupled receptors were identified in 9 out of 11 patients. The authors concluded that elimination of agonistic autoantibodies by immunoabsorption may relieve immune-mediated vasospasm and improve microcirculation [192].

Endovascular directional atherectomy

Successful use of Silver-Hawk directional atherectomy in two TAO patients with popliteal occlusions was recently reported; however, this endovascular procedure requires further validation by larger studies [193].

Growth factors

Basic fibroblast growth factor and vascular endothelial growth factor (VEGF) may play a role in patients with critical limb ischemia due to Buerger's disease. Isner and colleagues treated seven limbs in six patients with TAO (three men, three women; mean age, 33 years) in an open-label, dose-escalating, phase 1 clinical trial to document the efficacy and safety of gene transfer of naked plasmid DNA encoding VEGF (phVEGF165) via intramuscular injection in the treatment of critical limb ischemia [194]. Ulcers, which had not healed for more than 1 month before therapy, healed completely in three of five limbs after intramuscular phVEGF165 gene therapy. Nocturnal pain at rest was relieved in the remaining two patients, although both continued to have claudication. Two patients with advanced distal forefoot gangrene ultimately required below-knee amputation despite evidence of improved perfusion. This report suggests that angiogenesis induced by phVEGF165 gene transfer may provide an effective therapy for patients with advanced TAO that is unresponsive to standard interventions [194]. Another study demonstrated higher VEGF plasma levels in patients with TAO compared with controls ($P = .008$), showing the existence of a natural defense mechanism for ischemia and new collateral formation [195]. A recent phase I/IIa open-label four dose-escalation clinical study assessing the safety, tolerability, and efficacy of a single intramuscular administration of DVC1-0101 in patients with PAD also involved two patients with TAO [196]. DVC1-0101 is a new gene transfer vector based on a nontransmissible recombinant Sendai virus (rSeV) expressing the human fibroblast growth factor-2 (FGF-2) gene (rSeV/dF-hFGF2). The investigators concluded that DVC1-0101 was safe, effective and resulted in significant improvements of limb function [196].

Stem cell-based therapeutic angiogenesis

Angioblasts isolated from peripheral blood or bone marrow-derived endothelial progenitor cells (EPCs) can be incorporated into sites of active angiogenesis, providing a key factor in re-endothelialization [197]. Culture-expanded EPC transplantation in an animal model of limb ischemia improved neovascularization and blood flow recovery and reduced limb necrosis and autoamputation by 50 % compared with controls [198]. Preclinical [199] and clinical studies in patients with peripheral

artery disease and CLI [200], including TAO, suggest that the implantation of autologous bone marrow mononuclear cells [201–204], autologous peripheral blood stem cells [205, 206], mesenchymal stem cells derived from human umbilical cord blood [207], autologous adipose tissue-derived stem cells [208], and autologous whole bone marrow stem cells [209] into ischemic limbs can restore limb function by increasing new collateral vessel formation [210]. We and our colleagues have also demonstrated that the implantation of autologous bone marrow mononuclear cells in the ischemic limbs of patients with TAO is associated with improved rest pain scores ($P < .0001$), peak walking time ($P < .0001$), quality of life ($P < .0083$), and augmentation of collateral formation at 24 weeks in 78 % of patients [202, 211, 212]. Healing of ischemic ulcers was achieved in 83 % of the study group. Subsequent studies and meta-analysis supported intramuscular bone marrow cell administration as a relatively safe, feasible, and potentially effective therapy in patients with critical limb ischemia and TAO [210, 213]. Bone marrow-derived mononuclear cell therapy induced long-term improvement leading to an amputation-free rate of 91 % (95 % CI 82–100 %) at 3 years in the Therapeutic Angiogenesis by Cell Transplantation (TACT) Trial [214]. A combined approach of intra-arterial and intramuscular injections may maximize the chances of local deposition of stem cells in the ischemic limb [215].

Another method of stimulating angiogenesis by inserting intramedullary K-wires has been suggested by Inan and associates [216]. Fenestration of the tibia at six sites with EPC mobilization from bone marrow using recombinant human granulocyte colony-stimulating factor was reported recently by Kim and associates in 27 patients (34 lower limbs) with Buerger's disease [217]. Over a mean follow-up period of 19 months, 13 of 17 limbs with nonhealing ulcers healed. This technique resulted in a similar degree of new vascular collateral network development [217] compared with autologous bone marrow mononuclear cells aspirated from the iliac crest and implanted into the intermetatarsal region, the gastrocnemius muscle, and the dorsum of the foot or forearm [202]. Recently, functional impairment of endothelial progenitor cells was confirmed in TAO patients compared to healthy nonsmokers and smokers [218]. Ongoing work is focused on understanding the mechanisms of therapeutic angiogenesis, including vascular stem cell niches, mobilization, homing, and vascular repair [219].

Conclusions

Buerger's disease is an incredibly challenging disease with regards to both diagnosis and therapy. There is no gold standard for establishing the diagnosis of Buerger's disease, and even findings that are generally considered to be pathognomonic can be found in a broad range of rheumatic and non-rheumatic diseases. Tobacco cessation continues to be the cornerstone of therapy, although the options for such patients continue to grow steadily. Revascularization is often not an option for technical reasons. Endothelin

receptor antagonists and prostacyclins currently offer the greatest hope for such patients, although growth factor and stem cell-based therapies may someday join the standard of care as well.

Compliance with Ethical Standards

Conflicts of Interest

Ahmet Rüçhan Akar declares that he has no conflict of interest. Bahadır İnan declares that he has no conflict of interest. Çağdaş Baran declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

•• Of major importance

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