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Understanding Buerger's Disease: Symptoms, Diagnosis and Management Strategies

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Abstract:

Buerger's disease, also known as thromboangiitis obliterans (TAO), is a rare but serious condition that primarily affects the blood vessels in the limbs. This inflammatory vascular disease is characterised by the formation of blood clots in the small and medium-sized arteries and veins, which results in a reduction in blood flow. Patients typically present with symptoms such as pain in the extremities, ulcers, and in severe cases, gangrene. The disease is most commonly observed in young male smokers, which highlights the strong correlation between tobacco use and the onset of this condition.

A comprehensive understanding of Buerger's disease is essential for prompt diagnosis and effective management. This review will examine the historical context, symptoms, diagnostic criteria, therapeutic approaches, and future directions in research and treatment.

Keywords: Buerger's disease, thromboangiitis obliterans, vasculitis

Introduction:

Buerger's disease, also known as thromboangiitis obliterans (TAO), is a rare and severe form of peripheral vascular disease that predominantly affects the small and medium-sized arteries and veins in the extremities, particularly the hands and feet. (Olin and Shih, 2006) This condition is characterised by segmental inflammation and thrombosis, which result in progressive occlusion of the affected blood vessels and subsequent tissue ischaemia and necrosis.

The precise aetiology of Buerger's disease remains unclear; however, there is a strong association between tobacco use, particularly cigarette smoking, and the disease.

The clinical presentation of Buerger's disease is characterised by a wide range of symptoms, including intermittent claudication, rest pain, and ischemic ulcers or gangrene in the affected extremities.

Historical Background and Discovery:

The history of Buerger's disease can be traced back to the late 19th century. The initial description of thromboangiitis obliterans is attributed to Felix von Winiwarter, who in 1879 delineated a singular case of spontaneous gangrene resulting from intimal proliferation, which

he designated as "endarteritis obliterans" (von Winiwarter, 1879). Subsequently, the condition was clarified by the Austrian surgeon Felix Buerger in 1908 (Buerger, 1908). His observations of patients presenting with severe limb ischaemia and ulceration led him to identify a distinct vascular disorder with a common association between the disease and tobacco consumption. This condition was subsequently named in his honour.

Since its initial identification, the medical community has made significant advancements in elucidating the aetiology and progression of Buerger's disease. As research in this field continues, our understanding of Buerger's disease has expanded, resulting in the development of improved diagnostic criteria and therapeutic strategies.

Epidemiology and Risk Factors:

The disease typically affects individuals in their youth or middle age, with a higher prevalence among men compared to women. (Sharma et al., 2014) The incidence of Buerger's disease exhibits geographical variation, with higher rates reported in the Middle East, Asia, and the Mediterranean region compared to North America and Western Europe. (Sharma et al., 2014; Modaghegh and Saberianpour, 2021) Among certain ethnic groups, Ashkenazi Jews are predominantly affected, and the disease typically occurs in patients with a low social status. (Klein-Weigel and Richter, 2014) There is substantial evidence that smoking is a significant risk factor for the development and progression of Buerger's disease (Modaghegh and Saberianpour, 2021).

In addition to tobacco use, other risk factors may contribute to the development of Buerger's disease. Such factors include:

- Genetic predispositions may result in a heightened susceptibility to the disease in certain individuals. (Klein-Weigel and Richter, 2014)
- Exposure to cold temperatures, which can exacerbate symptoms.
- Other autoimmune conditions that may interact with vascular health.
- The role of hyperhomocysteinemia remains a topic of debate in the medical community, as it is a characteristic feature of atherosclerosis. (Liew et al., 2015).

Etiology and Pathophysiology:

The precise aetiology of the inflammatory response in Buerger's disease remains uncertain. However, it is hypothesised that tobacco-derived compounds may act as triggers in genetically susceptible individuals, with a pivotal role for autoimmune inflammation in the initiation and perpetuation of TAO activity. (Arkkila, 2006)

The most recent research findings indicate that the protein expressions of MyD88, TRIF and NF-κB are markedly elevated in the vascular endothelial and vascular smooth muscle cells of patients with TAO. These observations suggest that the TLR signalling pathway may play a pivotal role in the pathogenesis of TAO, thereby influencing the pathogenesis and progression of TAO. (Guo et al., 2024) These findings suggest that targeted therapy for the TLR signalling pathway may represent a promising avenue for therapeutic intervention in TAO.

The pathophysiology of Buerger's disease is typified by segmental vasculitis, which predominantly affects the small and medium-sized arteries and veins in the extremities and involves a complex interplay of inflammatory processes and vascular occlusion.

The key features of the pathophysiological mechanisms are as follows:

- **Inflammation:** Immune-mediated inflammation leads to endothelial damage, attracting leukocytes and causing thrombus formation.
- **Thrombosis:** The formation of blood clots results in occlusion of the affected vessels, leading to ischemia and subsequent tissue damage.
- **Vasospasm:** Episodes of vasospasm can occur, particularly in response to cold or stress, further exacerbating the ischemic process.

From a pathological perspective, TAO lesions can be classified into three categories: acute, subacute, and chronic. The latter category is indistinguishable from other forms of chronic arterial occlusive diseases. (Klein-Weigel and Richter, 2014) The acute-phase lesions comprise an occlusive thrombus with high cellularity and marked inflammatory activity, accompanied by a lesser degree of inflammation in the vessel walls. Polymorphonuclear leukocytes, microabscesses and multinucleated giant cells may be present. (Arkkila, 2006)

Clinical Manifestations and Symptoms:

The clinical manifestations of Buerger's disease are highly variable, with a wide range of symptoms that may vary in both severity and duration. The symptoms have the potential to significantly impact the quality of life, thereby necessitating prompt intervention to prevent

progression. It is therefore of the utmost importance to be able to recognise these symptoms at the earliest opportunity in order to ensure effective management.

The clinical symptoms typically manifest initially in the extremities, with a propensity for involvement of the hands and feet. The most frequently observed manifestations include:

- **Pain in limbs**

Patients often report intermittent claudication, characterised by pain during physical activity that resolves with rest. Additionally, they may experience numbness and/or tingling in the limbs (Arkkila, 2006).

- **Migratory superficial thrombophlebitis** (Del Conde and Peña, 2014)
- **Coldness in limbs**

Affected individuals may experience a sensation of unusual coldness in the affected areas, particularly in comparison to other parts of the body. Additionally, Raynaud's phenomenon may be observed.

- **Skin changes/ subungual and skin infection/ phlegmone/ acral skin discoloration**

The skin may display discolouration, such as pale or bluish hues, and may become shiny or hairless. A perspicacious evaluation of the nails may facilitate an early diagnosis, as early digital ischemia may manifest with decelerated nail growth, resulting in nail plate thickening and roughness with transverse or longitudinal ridging, splinter hemorrhages, and onychogryphosis. At a later stage, nail changes may include the development of Beau's lines, onychomadesis, or permanent dystrophy, which may result in the potential loss of the nail, ulceration and necrosis of the digit. A case of true leukonychia, characterised by a white discolouration of the nails, was reported in which the condition was isolated to the right second and third fingernails and presented as the initial symptom of early thromboangiitis obliterans (TAO). (Hamid et al., 2024)

- **Ulcers and gangrene**

In cases of severe ischemia, painful ischemic ulcers may develop on the fingers and toes, or even result in tissue necrosis. Such complications may necessitate surgical intervention, including amputation of the affected limb. The complications can significantly impair mobility and lead to chronic pain, significantly impairing a patient's quality of life.

It is worthy of note that a limited number of case reports have documented the presence of TAO in the male reproductive system, including the spermatic cord, penis, and testicle. (Harwood et al., 2023) Furthermore, TAO can result in **secondary infertility** due to

the presence of anti-sperm antibodies, disrupted genital circulation, autonomic dysfunction and impaired sperm motility. (Ziaeemehr et al., 2022)

Diagnosis:

Over time, a number of diagnostic criteria for TAO have been proposed, but none has been universally accepted as the gold standard. Consequently, the expert committees of the VAS-European Independent Foundation in Angiology/Vascular Medicine Working Group have provided practical recommendations on the diagnostic criteria for TAO, thereby facilitating their universal application. (Fazeli et al., 2023)

Criteria for '**definitive**' BD diagnosis:

- **history of tobacco smoking**
- **typical angiographic features** (normal proximal arterial structure, absence of atherosclerotic plaque/ microaneurysm, infra-popliteal arterial occlusion, corkscrew collaterals and skip lesions)
- **typical histopathological features** (intact internal elastic lamina, infiltration of polymorphonuclear inflammatory cells in all small and medium-sized vessels' wall layers)

A '**suspected**' diagnosis of BD is confirmed when a major criterion is present in conjunction with four or more minor criteria. In the absence of a major criterion, or in cases where fewer than four minor criteria are present, the utilisation of imaging and laboratory data may prove beneficial in facilitating the diagnosis.

Major criterium	The history of tobacco smoking.	
Minor criteria	Disease onset at age less than 45 years.	
	Ischemic involvement of **both** of the **lower limbs**	● absence of any distal pulses ● ankle brachial index (ABI) less than 0.9 ● Toe Brachial Index (TBI) (<0.75)

		● chronic sign of ischemia of either lower legs or feet in addition to the absence of any distal pulses of at least one limb
	Ischemic involvement of **any** of the **upper limbs**	● positive Allen's test ● absence of radial pulse ● Raynaud's phenomenon
	Thrombophlebitis migrans.	
	A red-blue shade of purple discoloration on edematous toes or fingers.	

Table. Major and minor criteria in VAS diagnostic criteria for Buerger's disease 2023 (Fazeli et al., 2023)

A number of diagnostic tests may be employed in order to confirm the diagnosis.

Test	**Description**
Angiography	Visualizes blood vessels and can show characteristic occlusions.
Doppler ultrasound	Assesses blood flow and detects abnormalities in vessels.
Biopsy of superficial thrombophlebitis	The typical histopathological features may be observed, which are characteristic of an acute phase lesion. This is defined as acute inflammation involving all layers of the vessel wall in association with occlusive cellular thrombosis and polymorphonuclear leukocytes with karyorrhexis, also known as 'microabscesses', which are present around the periphery of the thrombus. (Olin and Shih, 2006)

The angiographic features of TAO are typically characterised by a normal proximal arterial structure, the absence of atherosclerotic plaque or microaneurysms, infra-popliteal arterial occlusion, corkscrew collaterals and skip lesions. Corkscrew (CS) is a small arterial coiling that can be identified through the use of modern ultrasonographic techniques. It was previously only discernible through the use of angiography. (Homma et al., 2024)

Differential diagnosis:

Buerger's disease is a rare condition that can be challenging to diagnose, as it shares similar symptoms with other peripheral vascular diseases (Modaghegh and Saberianpour, 2021). The primary objective is to differentiate between Buerger's disease and other conditions that affect blood flow and can present with similar symptoms.

The following conditions should be included in the differential diagnosis (Qaja et al., 2023) (Del Conde and Peña, 2014):

- **Peripheral Artery Disease (PAD)**

The condition frequently presents with claudication and rest pain, which are similar to those observed in Buerger's disease. However, it is usually associated with atherosclerosis.

- **Raynaud’s Phenomenon and Scleroderma**

The condition is characterised by episodic vasospasm, which results in colouration changes, but lacks the inflammatory component that is typical of Buerger's disease.

- **Systemic Lupus Erythematosus (SLE)**

It has the potential to cause vascular inflammation; however, it typically presents with systemic symptoms and distinct serological markers.

- **Frostbite or Cold Injury**

May present with symptoms similar to those observed in digital ischemia, but is typically associated with a history of prolonged exposure to cold temperatures.

- **Vasculitis Syndromes**

In cases where the patient is younger, other vasculitis disorders such as giant cell arteritis or polyarteritis nodosa should be considered as a differential diagnosis.

- **Metabolic conditions**

TAO may present with symptoms similar to those of lower extremity ischemia in individuals with type 1 or 2 diabetes mellitus. Additionally, it can manifest with characteristics of painful inflammation, which is a hallmark of gout.

- **Antiphospholipid syndrome**
- **Drug induced vasculitis (e.g. cocaine, amphetamines)**

Therapeutic Approach:

The management of Buerger's disease involves a multifaceted approach, with a focus on **cessation** of smoking, which is the primary risk factor for the disease. (Modaghegh and Saberianpour, 2021)
The primary objective of Buerger's disease management is to provide symptomatic relief and to impede disease progression.

- Lifestyle Modifications:

It is strongly recommended that patients refrain from tobacco use and address other risk factors, such as hypertension and diabetes, in order to optimise their health outcomes. Regular exercise has been demonstrated to enhance circulation. Cessation of tobacco use has been demonstrated to result in notable amelioration of symptoms, including a reduction in claudication pain and an enhancement of blood flow. (Del Conde and Peña, 2014)

It is incumbent upon healthcare providers to underscore the significance of smoking cessation through the utilisation of an array of resources and support systems. Such programmes may comprise behavioural therapy, nicotine replacement therapies and counselling.

- Pharmacotherapy:

The administration of medications such as antiplatelet agents, vasodilators, and anticoagulants may be employed as a means of managing the symptoms and preventing disease progression. (Hill, 1974) Prostaglandin analogues (iloprost), cilostazol (a phosphodiesterase III inhibitor that acts as a vasodilator and exhibits weak antiplatelet activity and reduced blood viscosity) and bosentan can be administered. (Liew, 2015)

- Surgical Interventions:

In cases of severe critical limb ischaemia, revascularization procedures may be considered as a potential means of restoring blood flow. (Modaghegh and Saberianpour, 2021) Nevertheless, due to the distal localisation of arterial occlusions and the absence of recipient vessels, interventional or surgical revascularization is unfeasible in the majority of cases. (Klein-Weigel et al., 2014) The following strategies may be employed:

➔ **Endovascular angioplasty**

A meta-analysis of early and late outcomes following endovascular angioplasty in patients with thromboangiitis obliterans and chronic limb ischemia by Galyfos et al. (2023)

demonstrated that for patients with TAO and chronic limb ischemia, the procedure was associated with optimal safety and low complication rates comparable to those observed in patients who underwent open bypass surgery. The procedure was associated with a high level of safety, including a null in-hospital mortality rate and a very low perioperative complication rate. The incidence of complications was 1.9% for perforations, 2.2% for wound complications, and 0.2% for distal embolism. The limb salvage rate was 94.1% at 12 months and 89.1% at 36 months.

In light of these findings, it can be concluded that an endovascular approach may be a suitable first-line treatment option. However, it is important to note that many investigators will still offer angioplasty to patients with CLTI or recurrent symptoms after failure of conservative therapy, particularly in cases where surgical bypass is not a viable option. (Galyfos et al., 2023)

➔ **Bypass surgery**

Furthermore, critical limb ischemia may result in a significant **amputation**, with an elevated risk of amputation if the disease progresses. This risk is particularly pronounced in patients who continue to smoke. (Del Conde and Peña, 2014)

- Sympathectomy:

The laparoscopic lumbar sympathectomy and thoracoscopic sympathectomy, which are minimally invasive procedures, have been demonstrated to reduce digital pain and improve ulcer healing. A number of studies have demonstrated the safety and efficacy of both procedures in reducing pain and promoting healing in patients with Buerger's disease and peripheral arterial disease. This is due to the assumption that it has the potential to reduce peripheral retention, which is understood to be the cause of the opening of an arteriovenous anastomosis. This, in turn, results in an increase in blood flow to the skin tissue and subsequent vasodilatation. The results of the recent study by Hatta et al. (2023) concerning lumbal sympathetic block demonstrated the capacity of the procedure to impede the progression of TAO, diminish patient-reported symptoms, and facilitate wound healing. In addition to its inhibitory effect on vasomotor tone, neurolysis has also been demonstrated to attenuate the pain signal transmitted from the afferent nerve. Nevertheless, the role of sympathectomy in the treatment of Buerger's disease remains a topic of debate in the medical community, as there is currently a paucity of long-term data to confirm its efficacy. (Liew et al., 2015)

- Stem cell therapy:

Stem cell therapy is a common treatment for the promotion of angiogenesis in patients with non-reconstructable peripheral arterial disease. (Liew et al., 2015) Meta-analyses have confirmed the feasibility and safety of cell-derived therapies, as well as their positive therapeutic effects, including pain control, ulcer healing, pain-free ambulation, and amputation-free survival, in patients with critical limb ischemia. (Klein-Weigel and Richter, 2014)

- Psychological Care:

The psychological impact of Buerger's disease on patients can be significant and complex. The chronic pain, potential for disability, and lifestyle changes that accompany the disease often give rise to a range of emotional challenges, including feelings of frustration, anxiety, and depression. Such emotional responses are frequently attributable to the physical constraints and the social stigma associated with smoking-related ailments.

Moreover, the extant literature suggests the existence of psychiatric manifestations associated with TAO, although the precise prevalence remains uncertain. It is hypothesised that the prolongation of the functional disturbance may result in irreversibility, which can be observed in the brain blood vessels. This could potentially result in the onset of a polymorphic psychopathology of a wide-spectrum psychiatric nosology, encompassing primary diagnoses of schizophrenia, mania, manic-depressive psychosis, epileptic psychosis, auditory hallucinations, and psychomotor agitation. (Awara et al., 2023)

It is imperative that the psychological aspects of Buerger's disease be addressed in order to provide comprehensive care.

It is of the utmost importance for both patients and healthcare providers to have a clear understanding of the prognosis and psychological impact of Buerger's disease. Through early intervention, lifestyle modifications, and psychological support, individuals with Buerger's disease can navigate their journey with greater resilience and an improved quality of life.

Future Directions in Treatment:

As research progresses, future directions in the management of Buerger's disease may focus on immunomodulatory therapies. It is imperative that ongoing research be conducted in order to enhance our comprehension of Buerger's disease and its underlying pathophysiology. Future therapeutic strategies may potentially encompass biologic targeted therapies aimed at the underlying inflammation or cell-based therapies promoting vascular regeneration, which represents an exciting area of research.

A recent study has demonstrated that the administration of **endothelial growth factor** (VEGF) plasmids and the delivery of mononuclear cells from the patient's own bone marrow, which contain multipotent cells, can facilitate the avoidance of amputation through the expedited formation of collateral blood supply to an ischaemic limb. Gene therapy is a promising, safe, and effective method; however, potential late complications, such as age-related macular degeneration or malignancy, remain to be determined. (Barć et al., 2024)

A further crucial aspect of the therapeutic approach is the management of symptoms and the enhancement of the quality of life of patients. Komiya et al. (2023) put forth the proposition that **supervised exercise therapy** (SET) constitutes an efficacious intervention for the treatment of Takayasu's arteritis-induced intermittent claudication (IC). Such an approach may result in a reduction in pain and subjective symptoms in the patient, which ultimately contributes to an improvement in quality of life. Furthermore, bilateral interval (10 days apart) **chemical neurolysis of the stellate ganglion** in Buerger's disease involving both hands represents a safe and effective technique for controlling disease progression, managing pain, preventing cardiac complications, and avoiding recurrent laryngeal nerve-related complications. (Singh and Sonkar, 2024)

A double-blind, randomised study was conducted to investigate the effects of low-intensity pulsed ultrasound (**LIPUS**) on symptoms in peripheral arterial disease patients with Buerger disease. A significant reduction in pain intensity was observed on the visual analogue scale, accompanied by a notable increase in skin perfusion pressure. Given the absence of severe adverse effects in any of the patients, LIPUS can be regarded as a non-invasive, safe and effective option for improving symptoms in patients with Buerger disease. (Mohamad Yusoff et al. 2024)

Prognosis and Disease Progression:

It is therefore crucial to diagnose and intervene at an early stage in order to optimise the prognosis for TAO. The degree of disease progression at the time of diagnosis has been demonstrated to have a significant impact on the prognosis for patients. (Bae et al., 2023)

The prognosis of Buerger's disease is largely dependent on the cessation of risk factors, particularly smoking. Patients who cease smoking may observe a notable improvement in both the severity of their symptoms and their overall health. Conversely, the continued use of tobacco can result in the development of severe complications, including critical limb ischaemia and the potential for amputation.

As the disease progresses, patients may experience an exacerbation of symptoms, including pain, ulceration, and gangrene, particularly in the extremities. In some cases, this may result in the necessity for amputation of the affected limb.

Current Research and Future Directions:

The research into Buerger's disease has increasingly concentrated on gaining insight into its underlying pathological processes, the role of the immune system in vascular inflammation and the development of innovative therapeutic strategies. To illustrate, Mashhadi et al. (2023) propose that the increased frequency of CD4+CD57+CD153+, CD4+CD57-CD153+, and CD4-CD57-CD153+ T (CD3+) cells observed in patients with TAO may be indicative of a role for cellular senescence in the disease process. A more comprehensive investigation into the underlying causes, prevalence and progression of immunosenescence in patients with TAO could potentially pave the way towards the development of novel therapeutic strategies for this disease. In this context, senolytic drugs may offer a promising avenue for the clearance or rejuvenation of senescent cells, thereby preventing disease progression. A further recent study by Öztan and colleagues (2023) conducted a comparative analysis of pathways associated with the immune system, cellular responses to stress, cytokine signalling in the immune system, and signalling by ROBO receptors between TAO patients and healthy controls. The expression of RPL27A, FMNL1, EIF4A1, RNF149, and EIF4G2 was found to be elevated in TAO patients, while PLP2, CCL4, EGR1, RPL9, LAMP2, and DGKZ exhibited decreased expression. These observations indicate the possibility of an association between these genes and the progression of TAO. The authors posit that by elucidating the protein expression levels of the genes that have been identified as key players in the molecular pathogenesis of TAO disease, it will be possible to ascertain the diagnostic and predictive utility of these selected transcripts. It is hypothesised

that these results will contribute to a greater understanding of the disease's pathophysiology. Furthermore, the identified candidate biomarkers have the potential to facilitate personalised medicine and new targeted treatments.

One promising direction is the exploration of **biomarkers** that could aid in the early diagnosis of Buerger's disease. Identifying specific markers in the blood may provide insights into the disease's progression and response to treatment. In a recent study, Zhang et al. (2024) sought to elucidate the causal impact of circulating inflammatory proteins on TAO. The analysis indicated C–C motif chemokine 4 (CCL4) and glial cell line-derived neurotrophic factor (GDNF) as potential protective biomarkers for TAO, whereas C–C motif chemokine 23 (CCL-23) emerged as a suggestive risk marker. These findings emphasise the importance of these proteins in the aetiology and potential future therapeutic strategies for TAO, as well as their role as potential biomarkers for TAO.

Furthermore, ongoing clinical trials are assessing the efficacy of various pharmacological interventions, including anti-inflammatory agents and therapies aimed at improving blood flow.

Another critical area of research is the impact of lifestyle modifications on disease management. As smoking cessation remains the cornerstone of treatment, studies are evaluating behavioral interventions that can support patients in quitting tobacco use. Some observational epidemiological studies have indicated a potential correlation between the **gut microbiota** and TAO. However, the precise causal relationship remains uncertain and represents a promising avenue for further investigation. In a recent study, Sheng et al. (2024) proposed that Ruminiclostridium and Lachnospira may have a protective effect on TAO, while Eubacterium (xylanophilum group) may have a risk effect on TAO. These findings indicate that specific microbiota are causally related to BD, suggesting their potential significance for the prevention and treatment of the condition.

Additionally, advancements in regenerative medicine and vascular surgery techniques hold promise for improving outcomes in patients suffering from severe complications associated with Buerger's disease.

Conclusions:

Buerger's disease is characterised by a set of specific symptoms, including pain in the extremities, the formation of ulcers and the potential for tissue necrosis. It is imperative that

these symptoms be identified promptly in order to facilitate an accurate diagnosis. The capacity to identify and respond rapidly can have a substantial influence on patient outcomes.

The diagnostic criteria frequently entail a combination of clinical evaluation and imaging studies, such as angiography, to assess vascular changes. It is of the utmost importance that healthcare professionals consider the possibility of Buerger's disease, particularly in young patients with a history of smoking and vascular symptoms. An effective approach to management necessitates a multidisciplinary approach, combining medical and behavioural strategies.

The most recent research offers promising prospects for the development of innovative therapies that target the disease's underlying mechanisms. It is possible that in the future, an emphasis on personalised medicine may result in the development of more bespoke treatment protocols for individuals diagnosed with Buerger's disease. Moreover, ongoing research into genetic factors and immune responses offers the potential for the development of targeted therapies that could alleviate symptoms and prevent disease progression.

In conclusion, the management of Buerger's disease is contingent upon the cessation of smoking and the fostering of awareness regarding the potential complications associated with the disease. The integration of multidisciplinary approaches, combining medical treatment with psychological support, is being emphasised as a means of enhancing the overall management of Buerger's disease. It is of the utmost importance to remain informed about the evolving landscape of this disease as new research findings emerge, in order to enhance patient outcomes.

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