



Review

Angiogenic therapy in peripheral arterial disease with granulocyte colony-stimulating factor (G-CSF)

La terapia angiogénica en la enfermedad arterial periférica con factor estimulante de colonia de granulocitos (G-CSF)

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Abstract

Introduction: peripheral arterial disease (PAD) is a chronic vascular condition characterized by progressive obstruction of limb arteries and is associated with high morbidity and mortality. Many patients are ineligible for revascularization, prompting the development of alternative alternatives such as angiogenic therapy.

Method: a systematic literature review was conducted in international databases (PubMed, Scopus, Web of Science, Cochrane and SciELO) using MeSH and DeCS terms related to angiogenic therapy, PAD, G-CSF, and stem cells. Articles published between 2015 and 2025 were selected, prioritizing relevant clinical trials and reviews.

Results: angiogenic therapy with granulocyte colony-stimulating factor (G-CSF) has demonstrated the ability to mobilize progenitor cells and promote neovascularization in both preclinical and clinical studies, resulting in improved perfusion and functional outcomes in ischemic tissues. Clinical studies have reported increased walking distance and reduced ischemic pain; however, uncertainty remains regarding durability of effect and optimal patient selection. The safety profile of G-CSF is favorable, with predominantly mild and transient adverse events.

Conclusions: granulocyte colony-stimulating factor (G-CSF) represents a promising and safe therapeutic option for patients with advanced PAD who are not candidates for revascularization. Its use should be individualized, and further studies are required to establish optimal treatment protocols and confirm long-term efficacy.

Keywords:

Angiogenic therapy. Peripheral arterial disease. Granulocyte colony-stimulating factor (G-CSF). Stem cells.

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Resumen

Introducción: la enfermedad arterial periférica (EAP) es una patología vascular crónica caracterizada por la obstrucción progresiva de las arterias de las extremidades, asociada a alta morbilidad y mortalidad. Muchos pacientes no son candidatos a revascularización, lo que ha impulsado el desarrollo de alternativas innovadoras, como la terapia angiogénica.

Método: se realizó una revisión sistemática de la literatura en bases de datos internacionales (PubMed, Scopus, Web of Science, Cochrane y SciELO) utilizando términos MeSH y DeCS relacionados con terapia angiogénica: EAP, G-CSF y células madre. Se seleccionaron artículos publicados entre 2015 y 2025, priorizando ensayos clínicos y revisiones relevantes.

Resultados: la terapia angiogénica con factor estimulante de colonia de granulocitos ha demostrado, en estudios preclínicos y clínicos, la capacidad de movilizar células progenitoras y de estimular la formación de nuevos vasos sanguíneos, mejorando la perfusión y la función en tejidos isquémicos. Los resultados clínicos han mostrado mejoras en la distancia de marcha y en la reducción del dolor isquémico, aunque persisten dudas sobre la duración de los efectos y la selección óptima de pacientes. La seguridad del G-CSF es favorable, con efectos adversos leves y transitorios.

Conclusiones: el G-CSF representa una opción innovadora y segura para pacientes con EAP avanzada no candidatos a revascularización. Sin embargo, su uso debe individualizarse y requiere más estudios para definir protocolos óptimos y confirmar su eficacia a largo plazo.

Palabras clave:

Terapia angiogénica. Enfermedad arterial periférica. Factor estimulante de colonia de granulocitos (G-CSF). Células madre.

INTRODUCTION

Peripheral arterial disease (PAD) is a chronic vascular condition characterized by the progressive obstruction of the arteries of the extremities, primarily the lower limbs, leading to a significant reduction in blood flow and high morbidity associated with pain, intermittent claudication, and, in advanced cases, critical limb ischemia. This condition affects millions of people worldwide, and its prevalence increases with age and the presence of risk factors such as diabetes, hypertension, and smoking, making it a relevant and steadily growing public health problem (1).

The conventional management of PAD includes lifestyle modifications, pharmacological therapy, and revascularization procedures, either surgical or endovascular. However, a significant proportion of patients are ineligible for these procedures due to the extent of the disease, comorbidities, or unfavorable vascular anatomy, which limits therapeutic options and leaves these individuals at risk of major amputation and premature mortality (2).

Given these limitations, biomedical research has explored innovative alternatives, among which angiogenic therapy has gained particular interest. This strategy aims to stimulate the formation of new blood vessels (angiogenesis) to restore tissue perfusion in ischemic areas, harnessing the regenerative potential

of the organism through the administration of growth factors, progenitor cells, or gene therapy (3).

Granulocyte colony-stimulating factor (G-CSF) is a hematopoietic cytokine traditionally used to induce the proliferation and differentiation of neutrophils in patients with neutropenia. However, recent studies have demonstrated that G-CSF has additional properties, including the mobilization of hematopoietic stem cells and endothelial progenitor cells from the bone marrow into the peripheral circulation, which may promote angiogenesis in ischemic tissues (4).

The administration of G-CSF in animal models of ischemia has shown encouraging results, with increased capillary density, improved perfusion, and reduced tissue damage. These findings have driven the translation of this therapy into the clinical setting, especially in patients with advanced PAD who do not respond to conventional interventions (5).

The mechanisms of action of G-CSF in PAD appear to be related both to the mobilization of progenitor cells and to the modulation of the inflammatory microenvironment and the promotion of the secretion of other endogenous angiogenic factors, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) (6).

Recent clinical trials have evaluated the safety and efficacy profile of G-CSF in patients with PAD, reporting improvements in walking distance, reduction of

ischemic pain, and, in some cases, a decrease in the need for amputation. However, results have not always been consistent, highlighting the need for additional studies to identify the patient subgroups that benefit most from this intervention (7).

The safety profile of G-CSF in the context of PAD has generally been favorable, with mild and transient adverse effects such as fever, bone pain, and leukocytosis. Nevertheless, careful monitoring is essential, especially in patients with a past medical history of hematological or cardiovascular diseases, to minimize potential risks (8).

One of the main advantages of G-CSF therapy is its ability to be combined with other angiogenic strategies, such as the administration of autologous mononuclear cells or gene therapy, which could enhance the beneficial effects on neovascularization and functional recovery of ischemic tissues (9).

The role of biomarkers in predicting the response to G-CSF is currently under active investigation, as the identification of specific molecular profiles could optimize patient selection and personalize interventions, increasing efficacy and reducing risks (10).

G-CSF-induced mobilization of progenitor cells not only contributes to angiogenesis but may also exert immunomodulatory and anti-inflammatory effects, which could be relevant in the context of PAD, where chronic inflammation plays a central role in disease progression (11).

Despite these advances, questions remain regarding the durability of the angiogenic effects of G-CSF, the optimal frequency of administration, and its interaction with other pharmacological treatments, which requires long-term follow-up studies and larger controlled trials (12).

International clinical practice guidelines still consider angiogenic therapy with G-CSF to be experimental. They recommend its use within well-designed clinical trials and in patients with advanced PAD who are ineligible for conventional revascularization, emphasizing the importance of continued research in this field (13).

The development of new formulations and administration regimens of G-CSF, as well as the integration of advanced imaging technologies to monitor neovascularization, represent promising areas that could improve the efficacy and safety of this therapy in the near future (14).

The objective of this article is to evaluate and synthesize the current scientific evidence on the efficacy, safety, and clinical applications of angiogenic therapy with granulocyte colony-stimulating factor (G-CSF) for the management of PAD to identify its potential benefits, limitations, and future research areas to optimize its implementation in clinical practice.

METHODS

This research follows a bibliographic documentary methodology. For the collection, selection, evaluation, and analysis of updated information from articles obtained from Cuban and international journals, internet searches were conducted in different repositories using meta-search engines indexed in electronic databases such as PubMed, BVS, Google Scholar, Scopus, Web of Science, Cochrane, LILACS, MEDLINE, ScienceDirect, SciELO, and Redalyc, employing various Boolean operators as documentary sources on the topic addressed. Keywords verified in MeSH and DeCS were used: "angiogenic therapy," "peripheral arterial disease," "gene therapy," "growth factor," and "stem cells." A search limit was established with inclusion criteria focused on therapeutic angiogenesis in peripheral arterial disease, yielding a total of 40 articles, of which 22 were selected, including 9 published in Spanish and 13 in English.

RESULTS

PAD constitutes a clinical sign of atherosclerosis that predominantly affects the arteries of the lower extremities, leading to a progressive reduction in blood flow and high morbidity associated with symptoms such as intermittent claudication and critical ischemia. This condition is an important predictor of major cardiovascular events and is associated with a significant increase in long-term mortality (15).

The pathophysiology of PAD is characterized by the formation of atherosclerotic plaques that generate arterial stenosis and occlusion, thereby affecting distal perfusion. Factors such as hyperhomocysteinemia contribute to disease progression by promoting LDL cholesterol oxidation and reducing nitric oxide synthesis, exacerbating endothelial damage (16).

The prevalence of PAD ranges between 3% and 10% in the general population, increasing to up to 20% in individuals older than 70 years. This high prevalence, together with frequent underdiagnosis due to asymptomatic presentation in early stages, makes the use of non-invasive diagnostic methods such as the ankle-brachial index (ABI) essential for timely detection (17).

Early diagnosis of PAD is crucial to implement therapeutic strategies that prevent disease progression and reduce cardiovascular risk. The combined use of clinical tests, Doppler ultrasound, and segmental blood pressure measurements facilitates accurate assessment of vascular involvement (18).

Arterial obstruction in PAD is mainly due to atherosclerosis, which involves the accumulation of lipids and fibrous material in the arterial intima, resulting in reduced blood flow. This condition may present from asymptomatic forms to critical ischemia with tissue loss; intermittent claudication is the most common symptom (19).

Management of PAD includes stratification of global cardiovascular risk, since atherosclerotic disease affects multiple vascular territories. The coexistence of coronary and cerebrovascular disease in patients with PAD increases the risk of adverse events and requires a comprehensive approach (20).

Quality of life in patients with peripheral vascular diseases is significantly affected, especially in those with advanced symptoms. Functional limitation and chronic pain have a negative impact on daily activities and psychological well-being (21). International guidelines, such as those from the International Working Group on the Diabetic Foot (IWGDF), recommend a multidisciplinary approach for the prevention and management of PAD, emphasizing the importance of early detection and strict control of risk factors (22).

Angiogenic therapy has emerged as a promising alternative for patients with advanced PAD who are ineligible for conventional revascularization. This strategy aims to stimulate the formation of new blood vessels to improve tissue perfusion and prevent amputation (15). Granulocyte colony-stimulating factor (G-CSF) is a cytokine that mobilizes hematopoietic stem cells and endothelial progenitor cells from the bone marrow into the peripheral circulation, facilitating angiogenesis in ischemic tissues and promoting vascular repair (16).

Preclinical studies have demonstrated that the administration of G-CSF in animal models of ischemia increases capillary density and improves perfusion, in addition to reducing tissue damage, which has encouraged its clinical evaluation in patients with PAD (17). G-CSF-induced cellular mobilization not only promotes angiogenesis but also modulates the inflammatory microenvironment, stimulating the production of endogenous angiogenic factors such as VEGF and PDGF, which enhance neovascularization (18).

Clinical trials have reported that G-CSF therapy improves walking distance and reduces ischemic pain in patients with PAD, although results are heterogeneous due to differences in protocols and patient characteristics (19).

The safety profile of G-CSF has been evaluated in multiple studies, showing mild and transient adverse effects, such as fever and bone pain, without evidence of serious events related to its administration in the context of PAD (20).

The combination of G-CSF with other therapies, such as the administration of autologous mononuclear cells or gene therapy, has been explored to enhance angiogenesis and improve functional recovery in patients with critical ischemia (21). The identification of biomarkers that predict response to G-CSF is an area of active research, aiming to personalize treatment and optimize clinical outcomes in patients with PAD (22).

Chronic inflammation in PAD contributes to disease progression and endothelial dysfunction. The ability of G-CSF to modulate immune responses may be key to improving the tissue environment and promoting angiogenesis (15).

Questions remain regarding the duration of the angiogenic effects of G-CSF, the optimal frequency of administration, and its interaction with other pharmacological treatments, which requires longitudinal studies and larger clinical trials (16). Aggressive control of cardiovascular risk factors, such as smoking, diabetes, and hypertension, remains essential for the comprehensive management of PAD and should be complemented with innovative therapies such as angiogenic therapy (17).

Arterial hypertension is a factor that accelerates PAD progression and increases the risk of cardiovascular events. Recent studies suggest that stricter control may benefit certain subgroups of patients with PAD (18).

Pharmacological treatment with antiplatelet agents, statins, and antihypertensive drugs reduces the incidence rate of major cardiovascular events in patients with PAD, although its direct impact on angiogenesis is limited (19).

G-CSF therapy has demonstrated functional improvements in patients with PAD, reflected by an increase in maximum walking distance and a reduction in ischemic pain, contributing to improved quality of life (20). The combination of G-CSF with platelet-rich plasma and other regenerative factors has shown promising results in improving hemodynamic and clinical outcomes in patients with critical limb ischemia (21).

Advanced imaging modalities, such as magnetic resonance angiography and computed tomography, allow monitoring of G-CSF-induced angiogenesis and evaluation of the formation and functionality of new blood vessels (22).

The clinical application of angiogenic therapy with G-CSF should be individualized according to the clinical characteristics and degree of ischemia of each patient to maximize benefits and minimize risks (15). The combination of cellular and gene therapy with G-CSF opens new perspectives for achieving more robust and sustained angiogenesis, improving tissue survival and motor function in patients with PAD (16).

G-CSF-induced progenitor cell mobilization may exert beneficial systemic effects, contributing to vascular repair in other territories affected by atherosclerosis, such as the coronary and cerebral circulation (17). Systemic and local inflammation in PAD may be modulated by G-CSF therapy, which could contribute to the stabilization of atherosclerotic plaques and reduction of the risk of major cardiovascular events (18).

The establishment of standardized protocols for G-CSF administration and clinical follow-up is essential to evaluate its efficacy and safety in the routine clinical practice (19). Finally, angiogenic therapy with G-CSF represents a frontier in the treatment of PAD, with the potential to transform the therapeutic paradigm and offer new hope to patients with advanced disease, although further research is required for its definitive incorporation into clinical practice (20).

CONCLUSIONS

G-CSF therapy has the potential to transform the management of advanced PAD, offering a therapeutic option that may improve quality of life and reduce associated morbidity. The integration of angiogenic therapy with G-CSF into a multidisciplinary approach that includes strict control of cardiovascular risk factors, lifestyle changes, and personalized clinical follow-up is essential to maximize its benefits. However, its definitive incorporation into clinical practice requires larger controlled clinical trials and long-term studies to confirm its safety and efficacy profile.

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