Endothelin receptor antagonism – new perspectives in the treatment of systemic sclerosis

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Abstract

Endothelin-1 is a naturally occurring polypeptide which possesses a broad range of activities including vasospastic, proinflammatory and profibrotic properties. Systemic sclerosis is a multisystem connective tissue disease characterized by vascular damage, inflammatory infiltrates and progressive fibrosis of the skin and internal organs. The results of the recent studies indicate that endothelin-1 may be a key element of the pathogenesis of systemic sclerosis. Accordingly, new class of drugs, endothelin receptor antagonists have been introduced for treatment of patients with systemic sclerosis.

This article reviews the role of endothelin-1 in the pathogenesis of systemic sclerosis and the implications of endothelin receptor antagonism in the treatment of systemic sclerosis.

Key words: endothelin, endothelin receptor antagonism, systemic sclerosis.

Endothelin-1 in systemic sclerosis

Endothelin-1 (ET1) is a naturally occurring 21-aminoacid polypeptide [1,2]. ET1 was first identified in 1988 by a group of Japanese investigators as a product of endothelial cells [1,2].

ET1 possesses a broad range of biological activities. It is considered one of the most potent vasoconstrictors known [2]. ET1 is also involved in the proliferation of fibroblasts and smooth muscle cells through direct stimulation or potentialization of the effects of other growth factors. It has also been shown to stimulate fibroblast chemotaxis and induce extracellular matrix synthesis [2-5]. Recently, Shi-Wen et al. showed, that ET1 induces myofibroblast phenotype in cultured human fibroblasts [6]. Myofibroblasts, characterized by the expression of α-actin and higher collagen production are considered to be key cells responsible for the pathogenesis of fibrotic conditions such as systemic sclerosis (SSc) or pulmonary fibrosis. Finally, ET1 is also involved in the inflammatory response since it stimulates monocytes and neutrophils [1,7].

ET1 is involved in many physiological processes such as development of respiratory system, and cardiovascular homeostasis. Recently, ET1 has been implicated in the pathogenesis of several diseases [1].

SSc is a multisystem disease characterized by vascular changes, local inflammatory infiltrates and progressive fibrosis of the skin and internal organs. Vascular changes characteristic for SSc include Raynaud phenomenon, capillary angiopathy, ischemic ulcers and pulmonary arterial hypertension [8]. The latter one is considered to be the most fatal complication of SSc [9,10]. Scleroderma related interstitial lung disease, known also as pulmonary fibrosis or scleroderma related fibrosing alveolitis is another frequent and severe complication of SSc [11]. Unfortunately, there are no effective treatments for SSc patients so far, and the drugs that were shown to be of any therapeutic effect are very toxic.

It has been shown that ET1 levels are increased in patients with SSc compared to healthy controls. Interestingly, plasma/serum ET1 levels were shown to be higher in patients with diffuse cutaneous SSc compared to those with limited cutaneous SSc, and higher in SSc patients with fibrotic skin and lung changes compared to those without [1,12,13]. Elevated ET1 levels were also reported in bronchoalveolar lavage (BAL) fluid from patients with SSc and breath condensate from patients with interstitial lung diseases including these with scleroderma related fibrosing alveolitis [14-16]. In the study by Cambrey et

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al. ET1 was responsible for approximately 40% of BAL fluid mitogenic activity for fibroblasts [14]. It has also been shown that ET1 is overexpressed in the skin and the lungs of patients with SSc compared with healthy controls [17,18]. In vitro studies showed that fibroblasts cultured from patients with SSc display enhanced ET1 expression [19]. Accordingly, exposure of normal human fibroblasts to ET1 caused phenotypic changes typical for SSc-derived fibroblasts [3,6].

Endothelin-1 receptors

There are two separate ET1 receptors identified: ETA and ETB. Both receptors belong to the superfamily of 7-transmembrane G-protein-coupled receptors but can mediate different, sometimes opposing, effects. ETA and ETB show tissue-specific pattern of expression [1,2]. ETA receptors are abundantly expressed on the vascular smooth muscle cells, where they are responsible for the vasoconstictive action of ET1. ETB receptors are also found on the vascular smooth muscle cells where they produce vasoconstriction. However, ETB receptor expressed on endothelial cells stimulate production of vasodilatatory compounds, such as prostacyclin and nitric oxide and mediate endothelium-dependent vascular relaxation [1,2].

Both ETA and ETB receptor were shown to be involved in the ET1-mediated cell proliferation. Experimental data indicate that ETB receptor is responsible for profibrotic and pro-inflammatory effects of ET1 [2].

It has also been shown that expression of ET1 receptors is dysregulated during different disease states. Expression of ETA receptor was reduced in SSc fibroblasts by 50% [3]. Similarly, ETA expression was shown to be significantly reduced and ETB upregulated in SSc associated lung fibrosis when compared with healthy lung [18]. Endothelial ETB receptors are down-regulated in diseases associated with endothelial dysfunction whereas intimal, smooth muscle ETB receptors are up-regulated in several vascular diseases including pulmonary arterial hypertension [2].

Endothelin receptor antagonists (ERAs) – new perspective in the treatment of patients with systemic sclerosis

Discovery of ET1 receptors allowed ET receptor antagonists (ERA) to be developed. Bosentan, which is orally active, dual (nonselective) ET receptor antagonist, was the first ERA tested in clinical trials. The results of two double-blind, placebo-controlled clinical trials (study 351 and BREATH-1) showed that bosentan significantly improved exercise capacity and cardiopulmonary hemodynamics in patients with pulmonary arterial hypertension (PAH) compared to placebo [20-22]. Since PAH is relatively frequent complication of SSc, the above mentioned clinical trials included also patients with SSc-related PAH, 52 altogether (37 in bosentan arm and 15 in placebo arm of the study). Analysis of patients with SSc-related PAH revealed that overall effect was comparable to that seen in idiopathic PAH, however, beneficial effect of bosentan seen in patients with SSc-related PAH was mainly due to stabilization rather than improvement of their functional status. Accordingly, patients with SSc-related PAH who received placebo deteriorated during the study time [23]. It is known, that patients with SSc-related PAH had worse outcome than those with primary PAH [9].

The results of the above mentioned clinical studies allowed bosentan to be registered in the USA and European Union for treatment of severe PAH including SSc-related PAH. The advantages of bosentan is its oral administration as well as relatively lower treatment costs when compared to continues infusion of prostacyclin. This was the reason that the recent evidence-based treatment algorithm in pulmonary arterial hypertension mention bosentan as first-choice drug in patients with severe PAH, non-responding to acute vasodilatation [24].

Recently, a new selective ETA receptor antagonist, Sitaxsentan is under study in clinical trials with very promising clinical effects [25].

Another common manifestation of vascular disease in SSc patients are ischemic digital ulcers which cause pain and hand function impairment. The RAPIDS-1 study (Randomized, Placebo-Controlled Study on the Prevention of Ischemic Digital Ulcers secondary to systemic Sclerosis) was a double-blind placebo-controlled study designed to investigate the effect of bosentan in preventing ischemic digital ulcers in SSc patients. Bosentan significantly reduced the number of new ulcers, particularly in the high risk patients with digital ulcers at baseline. In patients receiving bosentan, a statistically significant improvement in hand function was also observed. However, there was no difference observed in the healing of existing ulcers between patients receiving bosentan and those receiving placebo [26].

Since there is evidence showing that ET1 may be involved in the pathogenesis of interstitial lung diseases, there are another clinical trials under way. BUILT-1 and BUILT-2 studies were designed to investigate clinical effects of bosentan in patients with idiopathic pulmonary fibrosis and SSc-retaled interstitial lung diseases, respectively. The first results of BUILT-2 trial are expected in the year of 2006. However, there are anecdotal reports showing improvement of skin fibrosis in SSc patients treated with bosentan [27].

Conclusions

In summary, ERAs are a new class of drugs which had already been proved to be effective in the treatment of vascular complications of SSc. There is hope that they may also be helpful in treating fibrotic complication of SSc. However, there is still a lot to be learnt about long-term effect and safety of these new drugs in SSc patients.

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