Bosentan effects in Raynaud’s Phenomen and digital ulcers in Systemic Sclerosis and very early Systemic Sclerosis patients

Background

Systemic sclerosis (SSc) is a multisystem disorder of unknown aetiology involving autoimmune mechanisms, which contribute to micro-vascular damage, and excessive accumulation of collagen and other extracellular matrix components in skin and internal organs. The disease is characterised by endothelia derangement (Raynaud’s phenomenon (RP) and digital ulcers (DU), hypertensive renal failure, cardiomyopathy, pulmonary hypertension) and organ fibrosis (skin thickening, pulmonary fibrosis, gastrointestinal dysmotility, myocardial fibrosis) (1).

At present, overt clinical SSc however is diagnosed according to the ACR criteria which require either the presence of skin sclerosis proximal of the MCP or MTP joints, or the presence of two of three secondary criteria (sclerodactily, digital ulcers, or lung fibrosis) (2). In order to overcome the limitations of the ACR criteria, LeRoy and others formulated criteria for limited forms of SSc which basically defines a group of pre-SSc (3). According to the LeRoy criteria, patients with lSSc must have Raynaud’s plus scleroderma-type nailfold capillary changes and/or autoantibodies. Patients with ISSc however, also may or may not later develop SSc (4).

In a recent Delphi exercise four signs/symptoms have been identified as necessary for the very early diagnosis of SSc: RP, puffy fingers, ANA, specific antibodies (anti-centromere antibodies, anti-topoisomerase I antibodies), and capillaroscopy. The experts have then identified as RP, ANA and puffy fingers as “red flags” of which at least two must be present to further determine, as diagnostic tools for the diagnosis, specific antibodies (anti-centromere antibodies, anti-topoisomerase I antibodies) and capillaroscopy. (5)

RP is transient digital ischemia that occurs on exposure to cold temperatures. The ischemic phase is marked by demarcated pale or cyanotic skin limited to the digits. The attack usually ends with rapid reflow of blood to the digits, which results in a red appearance of the digits. The prevalence of RP in the general population is approximately 3–5%. (6)

Primary RP is characterized by symmetric attacks; the absence of tissue necrosis, ulceration, or gangrene; the absence of a secondary cause; normal nailfold capillaries; a negative test for antinuclear antibody; and a normal erythrocyte sedimentation rate. Symptoms are generally mild, and the median age at onset is 14 years. In contrast with primary RP, a secondary cause is suggested by age of onset greater than 30 years; episodes that are intense, painful, asymmetric, or associated with ischemic skin lesions; concomitant symptoms suggestive of a connective tissue disease; specific autoantibodies; and evidence of microvascular disease on microscopy of nailfold capillaries. Up to 90% of patients with SSc have secondary RP.(6) Non pharmacologic therapy includes avoidance of cold
temperatures, emotional stress, and smoking. Pharmacologic therapy includes calcium-channel blockers, alfa-adrenergic blockers, angiotensin II receptor antagonists, topical nitroglycerin, and pentoxifylline. Despite therapy, some patients with severe attacks will develop intense pain, ulceration and ischemic skin lesions, and gangrene and may ultimately require therapy with intravenous prostaglandins.

DU s are a frequent complication in patients with SSc, with an estimated frequency of 17-30% (7,8). These ulcers are often extremely painful and can cause progressive digital shortening with significant impairment of hand function and activities of daily living. Therefore, prevention of digital ulceration may not only improve hand function but also the QoL. Very few drugs have been proved to have effect on ischaemic ulcers in secondary RP. In earlier studies, iloprost and its analogue epoprostenol have been reported to improve healing of DU and prevent development of new ulcers (9-11). However, both of these prostacyclin analogues have to be given intravenously under supervision in the hospital setting.

Rationale

Endothelins are one of the key molecular mediators in SSc that have an impact both on the vascular and fibrotic pathogenic process. The endothelins are a family of three vasoactive peptides ET-1, ET-2 and ET-3. ET-1 is the major endothelin isoform and is processed sequentially from a 212 amino acid pre-pro ET-1 to the 21 amino acid biologically active ET-1 by an endopeptidase and the ET converting enzyme. ET-1 mediates its biological effects via the ETA and ETB receptors that are expressed on various cell types. ETA is expressed on mesenchymal cells and ETB is expressed on endothelial cells. In SSc, the primary target cells for the activity of ET-1 are smooth muscle cells, endothelial cells, fibroblasts and macrophages. In smooth muscle cells it promotes vasoconstriction and results in proliferation and elevated production of the key profibrotic factors TGF-beta and PDGF. In fibroblasts, ET-1 increases ECM production and increases adhesion molecule expression facilitating leucocyte-fibroblast interactions [9]. ETB receptors are expressed on endothelial cells; and they can mediate vasodilation by the release of nitric oxide. ETB receptors are also present on smooth muscle cells; however, in this area they behave similarly to ETA receptors. In SSc patients ETB receptors are downregulated on endothelial cells diminishing their vasodilatory role, and on smooth muscle cells they are upregulated, contributing to cell proliferation, hypertrophy, inflammation, fibrosis and vasoconstriction. ET-1 is over-expressed in both early and late stage SSc. Increased expression of ET-1 and ET-1 receptors is detectable in pre-sclerotic and early diffuse skin lesions, and elevated levels of ET-1 have been found in the blood vessels, lungs, kidneys and skin of SSc patients. Serum ET-1 levels are elevated in SSc patients and correlate with the severity of skin involvement and pulmonary fibrosis. Elevated ET-1 levels were also reported in bronchoalveolar lavage (BAL) fluid from patients with SSc and breath condensate from patients with ILD associated with scleroderma. In vitro studies have shown that fibroblasts cultured from patients with SSc display enhanced ET-1 expression. Exposure of normal human fibroblasts to ET-1 caused phenotypic changes typical for SSc-derived fibroblasts.(12)
Bosentan is a dual endothelin receptor antagonist and the others selectively block the ETA receptor. Bosentan an orally active, dual ET receptor antagonist is the first ERA approved in 2001 which competitively antagonizes the binding of endothelin to both endothelin receptors ETA and ETB. Its efficacy for preventing and treating of ischaemic ulcers has been evaluated in two well-designed studies, named randomized placebo-controlled investigation of digital ulcers in scleroderma (RAPIDS)-1 and RAPIDS-2, and also on the basis of several clinical observations (13). The current data in the literature on the effectiveness of bosentan for Raynaud’s phenomenon report a significant reduction in the daily duration, number and severity of RP attacks(14-16).

**OBJECTIVE:**

**Primary endpoint:**
Evaluation of Raynaud’s phenomenon and healing of digital ulcers in SSc and very early SSc parients
- Raynaud Condition Score (RCS) : Frequency, severity and duration of Raynaud attacks
- Healing digital ulcers
- Visual analogue scale for pain (VAS)
- morphological changes of digital vessel (Videocapillaroscopy) (CSURI)
- Function (SHAQ) and quality of life (SF36)
- Time to control worsening of DU (TTCW)

**Secondary endpoint:**
- prevention of DU
- Safety
- Capillaroscopic modifications

**DESIGN**
A single center retrospective study
Duration: 12 months

- Group 1: 30 SSc patient treated with **Bosentan 125 mg** (twice daily) + **Sildenafil 20 mg** (three times daily)
- Group 2: 30 SSc patient treated with **ILOPROST e.v. (once weekly)**
- Group 3: 30 SSc patient treated with **Bosentan 125 mg** (twice daily) + **ILOPROST e.v.**
- Group 4: 30 SSc patient treated with **Bosentan 125 mg** (twice daily)
- Group 5: 30 SSc patient treated with **Sildenafil 20 mg** (three times daily)
• Group 6: 30 VEDOSS patient treated with **Bosentan 62,5 mg** (twice daily) + **Sildenafil 20 mg** (three times daily)
• Group 7: 30 VEDOSS patient treated with **ILOPROST e.v.** (once weekly)
• Group 8: 30 VEDOSS patient treated with **Bosentan 62,5 mg** (twice daily) + **ILOPROST e.v.**
• Group 9: 30 VEDSS patient treated with **Bosentan 62,5 mg** (twice daily)
• Group 10: 30 VEDOSS patient treated with **Sildenafil 20 mg** (three times daily)

*Other concomitant treatment*

**Use of the following treatments is NOT allowed after Visit 1:**

a) ciclosporina A  
b) glibenclamide

**Admitted concomitant medication in both arms:**
Calcium antagonist  
Pentoxifilline

**PATIENTS POPULATION**

**Inclusion Criteria:**

• All patients affected by RP:  
  According to the results of the Delphi technique, the following signs (red flags) must be positive to suspect a very early diagnosis of SSc:
  1. *Raynaud’s phenomenon, defined as episodic, bi or triphasic (pallor, cyanosis, redness) vascular reactions of the fingers, toes, ears or nose. In concordance with clinical care, a clinical diagnosis of RP based on patient reported symptoms is valid.*
  2. *ANA positivity $\geq 160 (1:160)$*

In these patients, puffy fingers, puffy fingers turning into sclerodactily, and specific antibodies (Anti-centromere ACA and Anti Scl 70 (Antitopoisomerase I) and naifold capillaroscopy will be investigated and, if positive, organ involvement will be investigated (heart, lung, kidney, gastrointestinal tract)
- Male and female adults aged ≥ 18 years, who have signed an Informed Consent Form prior to initiation of any study-related procedure.

- Patients with established SSc classified as SSc by the American College of Rheumatology (ACR) criteria; including all patients with any other connective tissue diseases (CTD) who, in parallel, meet the ACR criteria for SSc

**Exclusion Criteria:**

-Hypersensitivity to the active substance or to any of the excipients

- Moderate to severe hepatic impairment, i.e., Child-Pugh class B or C

- Baseline values of liver aminotransferases, i.e., aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT), greater than 3 times the upper limit of normal (see section 4.4)

- Concomitant use of cyclosporine A

- Pregnancy

- Women of child-bearing potential who are not using reliable methods of contraception

**Visit schedule and assessments**

At Visit 1, eligible patients commence therapy. Performed videocapillaroscopy (CSURI), RCSm HAQ, SF36 , TTCW

Patients will be visit at week 12 and week 24.

**Physical examination**

The investigator will perform a complete physical examination at each Visit. Significant findings that are present prior to the start of the study

**Laboratory Evaluations**

- Clinical chemistries: ALT, AST, γ-GT, serum creatinine, VES, PCR, total blood analyses

- pregnancy test (for females of childbearing potential)

**Function and Quality of Life**

The SHAQ and SF 36 will be self-administered by the patient at the investigator's site at baseline and at each monthly visit.
## Digital ulcers

### Prevention
- CSURI

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<td></td>
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<td>Early</td>
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<td></td>
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<td>Sclerodactily</td>
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Healing
- During the baseline visit assessing:
  - the duration of digital ulcers (time from their onset)
  - comorbidities;
  - concomitant medications.

During each visit patient advancement of hands’ skin disease will be directly assessed by a well trained physician: the degree of hands involvement will be classified into four levels:
- NO involvement
- Puffy hands
- Puffy hands turning sclerodactily
- Sclerodactily

Patients will be seen every 4 weeks for a period of 12 months and for each visit the following parameters will be assessed:

1. New Digital Ulcers
   - None
   - Only 1
   - From 1 to 3
   - More than 3

2. Gangrene
   - YES
   - NO

3. Amputation (surgical, auto-amputation)
   - YES
   - NO

4. Infection
   - None
   - Requiring systemic antibiotics
   - Osteomyelitis
   - Septicemia

5. Hospitalisation for DU
   - YES
   - NO

6. Pain
   - Not requiring medications
   - Requiring Non-opioids drugs
   - Requiring opioids

7. Dose escalation with vasodilators
   - YES
   - NO

8. Capillaroscopic sclerderma pattern
   - NO
   - Early
   - Active
   - Late

SCORE FROM 0 TO 24
According to this table, some parameters will be scored 0 or 3 meaning absence or presence (Gangrene, Amputation, Hospitalisation for DU, Dose escalation with vasodilators); other parameters will be scored from 0 to 3 according to their growing severity or clinical importance (New digital ulcers, Infection, Pain, Capillaroscopic scleroderma pattern).

every 12 weeks:

1. **CAPILLAROSCOPIC SCLERODERMA PATTERN**

Microangiopathy evolution score (Ann Rheum Dis 2008; Sulli A et al)

**SAFETY**

**Adverse events**

Adverse events will be recorded at each study visit.

**STATYSTICAL ANALYSIS**
Bibliografia

11) Badesch DB, Tapson VF, McGoon MD et al. Continuous intravenous epoprostenol for pulmonary
16) M E Hettema, D Zhang, H Bootsma and C G M Kallenberg Successful treatment of patients with severe secondary Raynaud’s phenomenon with the endothelin receptor antagonist bosentan Rheumatology 2006;45:iii45–iii48