Chapter 2
Therapeutic Evolution: A Professor's View

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Keywords Captopril • Immunosuppression • Pharmacotherapeutic approaches • Professor's view • Relaxin • Therapeutic evolution • Vascular component

My first encounter with systemic sclerosis (SSc) in medical school was the demonstration for our class by the professor at Malmö Jan Waldenström of a case of what he presented as Thibierge-Weissenbach's syndrome. Dr. Waldenström had a strong interest in connective tissue diseases and urged us to buy the then new textbook by Talbott and Ferrandis [1]. Some lessons were "systemic scleroderma is not a rare malady," the overlap with polymyositis, and of course the unknown cause. Much of the pathology was well described, including "scattered foci lymphocytic infiltration distributed perivascularly." All organ manifestations were described; including the GI tract "starvation…is a serious threat" However, the incapacitating occurrence of fecal incontinence present in one-third of patients [2] was not mentioned. The laboratory findings were mostly "silent," in contrast to SLE, where leucopenia, hypergammaglobulinemia, and the LE-cell phenomenon [3] excited our interest. SSc was just an exotic enigma to us, which we tried to avoid. The treatment recommended was to maintain nutrition, use physical therapy to counteract contractures, protect against cold. Medication included para-aminobenzoic acid, high doses of vitamin D, and glucocorticoids. The use of vitamin D is interesting in the light of several recent reports of very low serum levels, even in SSc patients on vitamin D supplementation [4, 5]. Surgical sympathectomy was tried, usually without much success. The multitude of pharmacotherapeutic approaches is illustrated in Table 2.1 showing drugs used in scleroderma.

Captopril: A Success Story

Scleroderma renal crisis (SRC) and its complications used to be a dominating cause of early death in SSc. The patients often presented with therapy resistant malignant hypertension. Evidence amounted in the mid 1970s that this was due to over-expression of renin-angiotensin pathway. The outcome of SRC was usually end stage renal failure or death. The prognosis changed dramatically with the advent of the ACE-inhibitor captopril [6]. Early intervention was essential but it was observed that even patients with profound acute renal insufficiency could regain a slow recovery of renal function and eventually be managed without hemodialysis or renal transplant [7]. Long-term survival, although improved, is still lower than in non-renal SSc. High age, possibly glucocorticoid therapy and delayed intervention and severe vascular histology are identified indicators of poor outcome [8, 9].

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J. Varga et al. (eds.), *Scleroderma: From Pathogenesis to Comprehensive Management*,
DOI 10.1007/978-1-4419-5774-0_2, © Springer Science+Business Media, LLC 2012

Table 2.1 Pharmacotherapeutic approaches

Vasoactive drugs	Phenoxybenzamine tolazoline, methyldopa, guanethidine, reserpine, nicotinic acid, procaine
Antiinflammatory	Salicylates, *p*-aminobezoic acid (PABA), indometacin, phenylbutazone, antimalarials, corticosteroids, azathioprine
Experimental	*Oedema reducing*: PABA, ε-aminocaproic acid, disodium edentate
	Hormones: Corticosteroids, relaxin, progesterone
	Lathyrogens: Penicillamine
	Immunosuppressives: Alkylating agents, azathioprine, colchicine

Adapted from Hughes [49]. With permission.

Colchicine, D-Penicillamine, and Cyclofenil

In the 1960s and 1970s, interest focused on the increase deposition of collagen and the upregulated synthesis in fibroblasts cultured from the skin. This led to use of D-penicillamine and colchicine, based on in vitro and in vivo animal studies [10, 11]. Colchicine was used in few patients, whereas D-penicillamine became a widely used anchor drug worldwide. The use declined rapidly after the publication of a negative 24 months double blind comparison between a low dose of 150 mg every other day and a full dose of 750 mg daily showed no significant differences, but more adverse reactions in the active arm [12]. This was an ambitious although not strictly placebo controlled NIH funded multicenter trial, but the disappointing result did not convince everybody [13]. D-penicillamine is a labile reducing sulfhydryl reagent. Its absorption and bioavailability is variable and strongly influenced by food intake and concomitant medications. Thus, it cannot be excluded that the drug could have shown efficacy if these factors had been considered, in higher doses had been used, or if a different a subset of patients had been targeted [14].

In 1974 Dr. Herbai working in Uppsala, Sweden, noted that a weak estrogen, cyclofenil, inhibited incorporation of sulfur into which was in clinical use as a weak estrogen labeled to stimulate ovulation, seemed highly beneficial in a male patient with SSc [15]. The rationale was that cyclofenil inhibited sulfur incorporation in rodent cartilage in doses that had no estrogenic effect. The inhibition of chondrocytes matrix protein production was later confirmed [16]. Additional open use seemed to support the original case report [17], whereupon the chairman of the department professor Bertil Hood urged me to investigate this further. We performed a 2×6 months double blind cross-over study in 36 patients, which showed non-convincing trends in favor of the drug [18]. We later performed a double-blind 2-year comparison with D-penicillamine and placebo, which showed no effect on skin but a suggestive beneficial effect on pulmonary function compared to placebo. There were however more adverse reactions to cyclofenil [19]. Thus, cyclofenil could safely be added to the list on obsolete drugs for SSc. Cyclofenil is no longer available and the company, Ferrosan, in Malmoe which developed it, was swallowed by Leo in Helsingborg, which was bought by Pharmacia in Uppsala became Pharmacia Upjohn which finally ended up with Pfizer. But it was the cyclofenil work started my interest in SSc and also resulted in a long-standing friendship with Dame Carol Black.

Relaxin: Promising, Expensive, and Disappointing

Relaxin is a pregnancy associated hormone which was isolated from corpora lutea more than 75 years ago in crude form. Its function is inter alia to widen the pre-term birth channel, and its potential usefulness as anti-fibrotic drug in SSc resulted in early trials, using parenteral administration of porcine relaxin [20]. In "modern" times Edward Amento using recombinant human relaxin could show in vitro decrease secretion of collagens from normal fibroblasts, stimulation of pro-collagenase, and abrogation of TGFb and IL-1b stimulation of collagen synthesis [21]. Mice with mutated relaxin gene develop skin and internal organ fibrosis which if not too advanced is amenable to treatment with human relaxin [22–24]. Based on these observations a controlled and dose finding study was performed indicating tolerability of doses up to 100 mg/kg [25]. A small randomized controlled trial using 25,100 mg/kg or placebo showed positive results on skin with the *lower* dose only [26]. A following phase III study comparing placebo with 10 and 25 mg/kg however found no differences after 24 weeks [27]. So ended another endeavor. Possible explanations could be occurrence of neutralizing antibodies, or more likely the fact that patients with SSc already have increased levels of relaxin in the circulation [28].

Immunosuppression: Methotrexate, Cyclophosphamide, Apheresis, Stem Cell Transplantation: Still in Development

Autoimmunity clearly is one component of SSc and consequently immunosuppressive therapy has been in wide use over the years. Glucocorticoids probably have only limited value and have not been assessed in controlled trials. They may as indicated increase the risk of SRC. Methotrexate has been tested in one Dutch and one Canadian trial and found to be marginally effective [29, 30]. Methotrexate is not much used in Scandinavia unless there is evidence of myositis.

Several early reports including one from our unit have indicated efficacy of cyclophosphamide in selected patients with diffuse SSc. Patients with high acute phase reactants appeared to respond best [31]. A large multicenter placebo controlled study did indeed confirm modest superiority at 12 months but the effect did not last and the toxicity was not negligible [32, 33]. This therefore was not very encouraging despite data indicating that the patients in the active arm experienced improved quality of life [34].

In 1981 we read a report of a small series of patients treated with a combination of high dose cyclophosphamide combined with glucocorticoids and plasmapheresis [35]. All patients showed objective improvement. Following this provocatively optimistic lead we performed a 2-year randomized study comparing immunosuppression alone with the combination with plasmapheresis. Although this was a small study we found significant improvement in pulmonary function measured as total lung capacity and static lung compliance improved ($p < 0.01$). In four patients the number of premature atrial or ventricular contractions at 24 h ECG monitoring decreased, as did the concentrations of immunoglobulins and ANA titers in serum. However it could not be ascertained whether the clinical improvement was associated with combined therapy or immunosuppressive drug treatment alone [36]. This approach has not been pursued further, perhaps explained by the limited feasibility of the plasmapheresis component over time.

Another approach which is under evaluation is a more profound re-programming of the immune system using autologous stem cell transplantation (HSCT). Case reports and open series of cases indicate possible beneficial effect, but the safety profile is less clear [37, 38]. Treatment related mortality remains a major problem with HSCT, and it seems to be related more to experience of the center than to methodology. Importantly it may relate strongly to the diagnosis and be higher in SSc than, for example, in multiple sclerosis [39]. This could in part be related to the higher age of the patients but also to the more systemic nature of SSc compared to multiple sclerosis. Two multicenter randomized long-term trials are now in progress, one in USA and one in Europe. The European ASTIS trial has completed inclusion of 150+ patients in the two arms, pulsed cyclophosphamide or HSTC, and the 2-year results will be available in 2012 [47].

Targeting the Vascular Component: Prostanoids, Endothelin Receptor Antagonists, and Phosphodiesterase Inhibitors

The traditional use of nitroglycerin to ameliorate Raynaud's was messy and ineffective. Calcium channel blockers were in wide use but had modest effect as confirmed in a Cochrane survey [40]. And these agents were ineffective against digital ulcers and internal organ morbidity. A major advance was the advent of injectable prostanoids. In Europe the stabilized prostacyclin iloprost became the dominating agent in the mid 1990s [41] showing good short term effects on pulmonary arterial hypertension (PAP) as well as on the healing of digital ulcers [42]. More recently, bosentan, an orally administered dual endothelin-1 receptor antagonist was shown to be effective and was soon in wide use. Great hopes were raised regarding this compound regarding disease modification. A third drug followed soon, sildenafil [43]. However, despite these substantial advances the 4-year survival in SSc patients with PAP remains low [48], and cardiopulmonary complications dominate mortality, so even in this area there is need for improvement.

Gastrointestinal Problems

Based on its extremely high prevalence, GI involvement in SSc deserves more attention. Dysmotility can cause dysphagia, gastroesophageal relux (GERD), constipation, bacterial overgrowth, and pseudoobstruction. Fecal incontinence occurs in one-third of patients. Pseudoobstriction may cause rupture in extreme cases. Malnutrition is not unusual. Pharmacotherapeutic interventions aiming at improving peristalsis include metoclopropamide, domperidone, prucalopride, tegaserod, and erythromycin. Metoclopropamide (Primperan) is an antagonist of the dopamine-2 and 5-HT_3 receptors. Extrapyramidal

symptoms can limit its use. Domperidon (Motilium) is another dopamide-2 receptor inhibitor which may be useful, although published evidence is scant [44]. Octreotide (Sandostin or Sandostin LAR) is a growth hormone antagonist, and has also been useful in severe cases of pseudoobstruction [44, 45]. An adverse effect is a tendency to develop hyperglycemia. Erythromycin is not only an antibiotic, it is also a motilin agonist. Cisapride (Prepulside) is an agonist of the 5-HT_4. It was effective but could cause serious arrhythmias and has been withdrawn. Prucalopride and Tegaserod (Zelmac)are newer 5-HT_4 agonists. Non-absorbable antibiotics should be used to treat bacterial overgrowth, but only for short periods.

Fecal incontinence is often overlooked but has a profound psychosocial impact and cause depression and lead to social isolation, but it can be ameliorated by sacral nerve stimulation [46].

Concluding Remarks

The impressive advances in understanding many of the pathogenic events in SSc dealt with in other parts of the book have resulted in a number of therapeutic approaches, some of which I have mentioned in this chapter. The rational goal of interfering with unphysiological TGFb signaling covered in other chapters is still elusive but hopefully on the horizon. Seen from the patient's perspective, the establishment of multidisciplinary multipurpose scleroderma clinics with medical specialists as well as allied health professionals is an essential component of optimal management of SSc today and in speeding translational research.

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