Professional Development Dermatology

UCD CHARLES INSTITUTE SEMINAR SERIES

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Getting to know scleroderma

Attendees at UCD's Charles Institute Seminar Series heard a presentation from dermatology specialist Dr Jacobo Elies on scleroderma and vasculopathy in autoimmune skin diseases

The Charles Institute, Ireland's national dermatology research and education centre, played host to a range of guest speakers who covered a variety of topics ranging from skin cancer to psoriasis, among others. The series, which was sponsored by RELIFE (part of the A.Menarini group), was designed to provide expert advice from a range of distinguished national and international experts in their respective fields and was chaired by Prof Desmond Tobin, Full Professor of Dermatological Science at UCD School of Medicine and Director of the Charles Institute of Dermatology. The seminars were broadcast to attendees with a special interest in dermatology in other locations, who accessed the talks remotely via an audio-visual link.

Attendees at the series heard a presentation from Dr Jacobo Elies PhD, Principal Investigator at the University of Bradford, UK, where he is investigating endothelial dysfunction in disease models. In his talk, Dr Elies explained that scleroderma is a multifactorial autoimmune skin disease characterised by tissue fibrosis and vasculopathy, and spoke about the molecular mechanisms in the early stage of the disease with special emphasis on the link between aberrant TGF-ß signaling and endothelial dysfunction.

He also introduced the regulatory role of caveolin-1 as a suppressor of TGF-ß signalling and outlined how down-regulation of caveolin-1, which is present in scleroderma, influences dermal fibroblast behaviour from a resident to a profibrotic phenotype. The latter is thought to be a mechanism responsible for endothelial dysfunction in the skin microvasculature, leading to vasculopathy in scleroderma.

Research

Dr Elies told the attendees: "I want to emphasise the importance of vasculopathy in autoimmune skin diseases, as well as the mechanisms that link the profibrotic profile of scleroderma with a lack of, or reduced, angiogenesis". He also summarised research work he conducted as an independent Research Fellow at the University of Leeds (UK) collaborating with Dr Francesco DelGaldo, as well as the first evidence to demonstrate a link between fibrosis, mainly driven by increased TGF-ß signaling in scleroderma, and impaired angiogenesis.

"The word 'scleroderma' is derived from the Latin for 'hard skin,' particularly in the fingers and limbs," said Dr Elies. "But another hallmark of this disease is early vasculopathy. A very common symptom in these patients is Raynaud syndrome, a condition in which altered spasm of the arteries affects blood distribution. In scleroderma, Raynaud syndrome is accentuated and increases the chances of developing digital ulcers. These ulcers do not heal properly and commonly show deposition of calcium and in the later stages, can lead to amputation, and are very difficult to manage."

Diagnosis of scleroderma can be complex and is usually made at a late stage in the condition, Dr Elies explained. "Scleroderma is a rare disease, with an incidence of 30-to-300 per million," he told the seminar. "Sometimes, a lack of familiarity with the disease can delay the diagnosis and unfortunately, at the moment the treatment is almost always palliative and we can only deal with the symptomatology of the disease." Dr Elies provided a brief outline of the therapies typically used in scleroderma, however "these drugs can be more effective in the different stages of the disease," he pointed out. "As the disease progresses, the immunosuppressive therapies become less effective. Management of the vascular damage becomes palliative — there are no drugs or treatments that can reverse the endothelial dysfunction that occurs in the early stages of the disease.

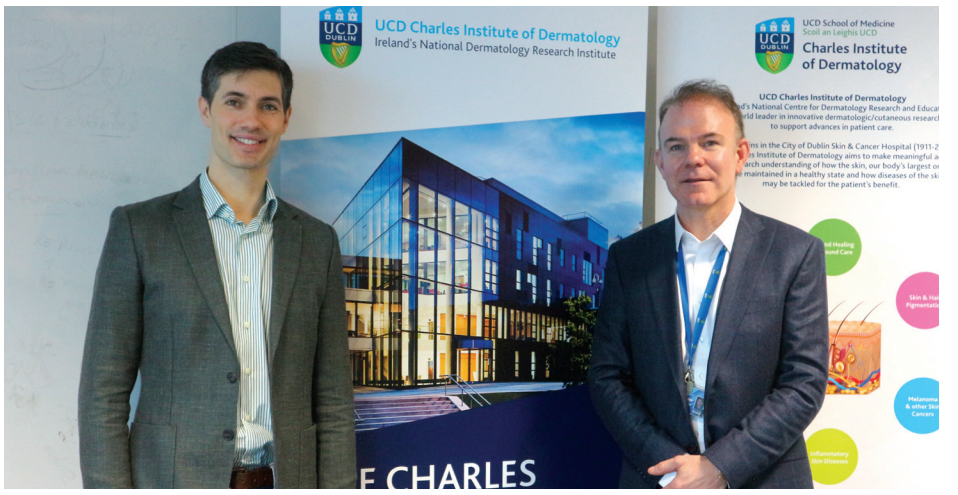
"Biologics are a relatively new type of drugs with enormous potential, however we are still waiting for evidence of how efficient these drugs will be [in scleroderma] and because of the high cost of these drugs, they are really only used in the very late stages of the disease." Last year, a multicenter randomized, double-blind phase 3 trial published in New England Journal of Medicine, showed that the biological Nintedanib (an antifibrotic treatment) reduced lung fibrosis in patients with ILD associated with scleroderma over a 1-year period (N Engl J Med 2019; 380:2518-2528. DOI: 10.1056/NEJMoa1903076). However, new therapies have been developed that act on new cellular targets, as well as new techniques such as optical coherence tomography, which helps to detect signs of pathology in the early stages of the disease, he explained.

In terms of the profibrotic profile and aetiology of the disease, Dr Elies told the seminar: "This is still not clear, but there are a few things that we do know," he said. "Scleroderma was originally considered a fibrotic disease," he said. "A lot of work has been done [to examine] elevated TGF-ß signalling as a growth factor and how this causes the fibrosis."

Fibroblasts

Presenting a synopsis of his research while at the University of Leeds, Dr Elies explained that the presence of scleroderma fibroblasts co-cultured with endothelial cells reduces both the number of tubular vascular formations and their length (parameters used to measure angiogenesis). "To establish whether pigmented epithelium-derived factor (PEDF) has a role in these structures, we basically silenced PEDF expression from the scleroderma fibroblasts," he said. "The co-culture of these fibroblasts reversed the impaired angiogenesis in comparison with co-cultures that contained native scleroderma fibroblasts. This is quite promising, because it actually shows a direct effect of PEDF in angiogenesis — when we silenced PEDF from the scleroderma fibroblasts, we observed a significant rescue of the tubular structure."

He also pointed out that caveolin-1 expression is down-regulated in scleroderma, which has been shown in lung biopsies, as well as skin biopsies and confirmed by Western Blotting. "Using skin biopsies, we showed that in scleroderma there is an inversed correlation in the expression of caveolin-1 and PEDF, so we wanted to see if there was a link between down-regulation of caveolin-1 and the PEDF-dependent impaired angiogenesis," he continued. "We still do not fully understand the TGF-ß receptor trafficking, but we do know that there are at least two pathways involved in receptor trafficking — one (dependent on clathrin) leads to profibrotic profile, whilst the other (dependent on caveolin-1) promotes degradation of the receptor, acting as a endogenous suppressor of TGF-ß signalling."



Dr Jacobo Elies (left) and Prof Desmond Tobin

Dr Elies summarised: "The results of our research indicate that hyperactive signalling of TGF-ß signalling can be regulated in scleroderma," although the exact mechanism remains somewhat unknown. "Hyperactive signalling of TGF-ß drives profibrotic and anti-angiogenic phenotypes. It can also be regulated by caveolin-1 as an endogenous mechanism for control," said Dr Elies.

He explained that his presentation was a brief whistle-stop tour that did not touch on some of the features of scleroderma, such as reactive oxygen species and oxidative stress in general, which are contributing factors to worsening of the disease "and play an important role in the interaction between fibroblasts and endothelial cells," said Dr Elies. "At the same time, there is immune dysregulation, different T-helper cells and macrophages that are producing large numbers of interleukins and growth factors that also modify the behaviour of endothelial cells and fibroblasts."

He explained that part of his current work is to further examine the mechanisms involved in the oxidative stress present in scleroderma.

Ulcers

During a lively Q&A session following the presentation, Prof Tobin raised the point with Dr Elies that digital ulcers caused by scleroderma are incapable of healing. "In addition to PEDF, there is an increase in collagen 1," Prof Tobin commented. "In wound-healing, you have to 'flip' between collagen 1 and collagen 3 in terms of their typical ratio, so is there a consequence in terms of collagen gene transcription here? In my experience, in highly-haired skin, scleroderma seems to be not quite so severe compared to other locations on the body — haired skin heals extremely well compared to non-haired skin.

"This suggests that availability of a collagen subtype may be very important — is scleroderma unusual in having an up-regulation of prototypic collagen 1, and are there other fibrotic diseases that have that intrinsic collagen 1 hyper-secretion?"

Dr Elies replied: "That is true — scleroderma tends to appear in less-densely haired areas… but healing is completely impaired in scleroderma; I don't think there is a 'switch' between the two collagen types and there is vasculopathy, so you don't get the necessary conditions to allow that tissue to regenerate."

Speaking to the ***Medical Independent (MI)*** following his presentation, Dr Elies expanded on the challenges in diagnosing scleroderma and why it is so often diagnosed late in the disease process. "Not many clinicians know this disease very well, as it is a very rare disease," he explained. "Also, the symptoms appear on the skin but there is often no connection made with what may be happening to the internal organs. Clinicians may only treat the digital ulcers and it is not until later that these other problems become evident. The ulcers may not be responding to normal therapy and the overall problems caused by the scleroderma may sometimes not be identified." This can be exacerbated by the fact that normally, patients will present to a dermatologist with the disease, rather than a rheumatologist, and scleroderma is classified as an autoimmune disease, he elaborated.

"Ideally, the dermatologist will suspect scleroderma while treating these digital ulcers and transfer the patient to the care of a rheumatologist," said Dr Elies.

"Another challenge is the heterogeneity of the disease," he told ***MI***. "Not all scleroderma patients show the same symptoms and the organ involvement may be different. In some, pulmonary hypertension may be aggravated by the disease, while in others there may be renal involvement, so all these complex factors make the disease very difficult to diagnose."

Immunologists also play an important role in the diagnosis and treatment of the condition, he added. "Therapies could be improved for scleroderma but I think this will change in the years to come. It is about knowing the immunological dysregulation in a particular type of tissue, and I think when we have this knowledge, it will become easier to manage the disease.

"The third challenge is achieving a very early diagnosis," he added. "Generally, it is diagnosed very late."

Dr Elies was also asked about any identifiable risk factors associated with the disease. "There are not really very common risk factors," he told ***MI***. "Normally, it is more common in women than men, in common with other rheumatoid diseases. The onset of the disease can occur at any stage of life but, the average patient is typically around 50 years old and postmenopausal age. It is for this reason that research on the potential therapeutic role of sex hormones is currently being conducted, — all of this adds to the difficulty in making an early diagnosis or identifying definitive risk factors."

RELIFE has had no input into the content of this article or series of seminars