scleroderma Voice Spring 2020

OUTCOME MEASURES AND ASSESSMENT IN JUVENILE SCLERODERMA.

Results of the Juvenile Scleroderma Workshops in Hamburg, Germany.

Juvenile systemic scleroderma is a very rare disease. According a recent publication[1], where the data of the administrative claims in the United States was used, the prevalence was approximately 3 per 1,000,000 children. The clinical characteristics of the pediatric disease are different from the adult disease. Around 75% of the pediatric patients have diffuse subset[2] shown in the juvenile scleroderma inception cohort (www.juvenile-scleroderma.com), compared to about 40% in the adult patients. The diffuse subset is considered more severe in adult population. In the pediatric population it seems to have a milder course. The 5 year survival with around 95% is significantly better than in adult patients with diffuse subset. In the pediatric population there are fewer differences between the diffuse and limited subset than in adult patients. The differences found, looking at the first 88 patients in the inception cohort, were as follows. Active digital tip ulcerations were present in 29% diffuse cutaneous juvenile systemic sclerosis and none in the limited cutaneous juvenile systemic sclerosis subjects ($p = 0.005$); of those with cardiopulmonary testing, 3% of diffuse subset patients and 23% of the limited subset patients had cardiac involvement ($p = 0.015$); pulmonary involvement is more frequent in the diffuse subset with 41% of compared with 22% of the limited subset ($p = 0.009$); physician global disease damage assessment was higher in the diffuse cutaneous juvenile systemic sclerosis group compared to the limited cutaneous juvenile systemic sclerosis group, 35 and 15 ($p = 0.021$).

We had 12 annual juvenile scleroderma workshops in Hamburg, Germany, organized by the author. All workshops were looking at updates and new developments regarding juvenile localized or systemic scleroderma. Based on this workshop, a guidance regarding diagnosis, follow-up and treatment for juvenile localized scleroderma was developed and published[3], which emphasized how to assess activity of the skin involvement using LoSCAT[4], and assessment of extracutaneous involvement, like arthritis, uveitis and CNS involvement. Another workshop looked at the important issue of how patients with Raynaud´s Phenomenon, the primary presentation of juvenile systemic scleroderma, should be followed. Here was stated, that the presence of antinuclear antibody (ANA) and nailfold capillaroscopy changes are strong risks to develop a connective tissue disease. These patients should be followed at least every 6 months to see early on if a defined connective tissue disease evolves[5]. It has to be mentioned that the pediatric norm values for nailfold capillaroscopy differ from adults, and this should be considered at the assessment[6].

In the last three workshops we looked at the

issue of how to adopt the modified Rodnan skin score (MRSS), an manual assessment method of the skin involvement. The MRSS is a pivotal outcome measure of every therapeutic trial of systemic scleroderma in adults. We suggested some modification of the adult assessment. As young healthy children have more subcutaneous fat tissue and this makes the skin more “bound” in a child. The subcutaneous fat tissue decrease over time, till it reaches the level of the adults. The normal skin score was defined in a child if the texture of the skin and feel of the skin is the same throughout the anatomic region and the mobility of the skin are symmetric. Additionally, there should not be secondary signs

of scleroderma. This definition is planned to be tested prospectively.

We looked at three main important issues of the description of the disease. How to assess activity, response and damage. These issues are important for clinical research, but for daily clinical practice, too. It is important to have a standardized assessment of the activity and damage of the disease to be able to compare response in different patient populations and to have a standardized assessment for Phase II, III (trials to license a medication for the treatment of the disease) and IV trials. At the meeting in 2018, we developed an activity score for juvenile systemic scleroderma patients. The activity score asses the degree of activity of the disease of all major organ systems, which are frequently involved, like skin, pulmonary involvement, cardiac involvement, gastrointestinal and musculoskeletal involvement. This activity score will be validated prospectively in the patients of the juvenile scleroderma inception cohort, where already over 150 patients are followed worldwide.

In 2018 we reviewed the proposed CRIS response index[7], too, which is recently used in adult systemic scleroderma trials and could be applied presumably in pediatric trials, too.

In 2019 December at the meeting we made a proposal for a damage index, similar to the activity index covering all important organ systems that are involved in juvenile systemic scleroderma. The pediatric damage index is an adaption of the previously developed and published damage index[8] for adult patients. This will be validated in patient populations of the juvenile scleroderma inception cohort.

Hopefully there will be a Phase II/III trial in juvenile systemic scleroderma, and we will have licensed medication for children and adolescents with this orphan disease. In these potential trials, the proposed instruments can be applied and tested. Until then it is important to have the standardized follow up in the juvenile scleroderma inception cohort (www.juvenile-scleroderma.com) and in the CARRA juvenile scleroderma cohort to learn more about this rare disease in childhood and be able to improve the outcome for the patients. Every patient included in the cohorts will help to increase our knowledge.

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References:

1. Beukelman T., Xie F., Foeldvari I. Assessing the prevalence of juvenile systemic sclerosis in childhood using administrative claims data from the United States. Journal of Scleroderma and Related Disorders. 2018;3(2):189-90.
2. Foeldvari I., Klotsche J., Torok K.S., Kasapcopur O., Adrovic A., Stanevica V., et al. Characteristics of the First 80 Patients at Timepoint of First Assessment Included in the Juvenile Systemic Sclerosis Inception Cohort. www.juvenile-scleroderma.com. Journal of Scleroderma and Related Disorders. 2019;4:49-61.
3. Constantin T., Foeldvari I., Pain C.E., Palinkas A., Hoger P., Moll M., et al. Development of minimum standards of care for juvenile localized scleroderma. Eur J Pediatr. 2018;177(7):961-77.
4. Arkachaisri T., Vilaiyuk S., Torok K.S., Medsger T.A., Jr. Development and initial validation of the localized scleroderma skin damage index and physician global assessment of disease damage: a proof-of-concept study. Rheumatology (Oxford). 2010;49(2):373-81.
5. Pain C.E., Constantin T., Toplak N., Moll M., Iking-Konert C., Piotto D.P., et al. Raynaud's syndrome in children: systematic review and development of recommendations for assessment and monitoring. Clin Exp Rheumatol. 2016;34 Suppl 100(5):200-6.
6. Piotto D.P., Sekiyama J., Kayser C., Yamada M., Len C.A., Terreri M.T. Nailfold videocapillaroscopy in healthy children and adolescents: description of normal patterns. Clin Exp Rheumatol. 2016;34 Suppl 100(5):193-9.
7. Khanna D., Berrocal V.J., Giannini E.H., Seibold J.R., Merkel P.A., Mayes M.D., et al. The American College of Rheumatology Provisional Composite Response Index for Clinical Trials in Early Diffuse Cutaneous Systemic Sclerosis. Arthritis Rheumatol. 2016;68(2):299-311.
8. Ferdowsi N., Huq M., Stevens W., Hudson M., Wang M., Tay T., et al. Development and validation of the Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI): a novel instrument to quantify organ damage in systemic sclerosis. Ann Rheum Dis. 2019;78(6):807-16.

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