Scottish Paediatric & Adolescent Rheumatology Network

Assessment and management of Juvenile Localised Scleroderma

NOTE

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined based on all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

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BACKGROUND

Juvenile localised scleroderma (JLS) is characterised by autoimmune inflammation and sclerosis of the skin and subdermal tissue. It is rare, has a wide spectrum of severity and can lead to significant morbidity. JLS can be subdivided into: linear scleroderma (most common, affecting one or more parts of the body), circumscribed morphoea, generalised morphoea, pansclerotic morphoea and a mixed subtype (2,3). It is more common in females and has a typical age of onset of 7yrs but can be present from birth. (4,5)

There are limited evidence-based guidelines for the assessment and management of JLS and clinical practice can vary considerably. Following a systematic literature review and experienced clinician discussion, a set of consensus-based management recommendations for JLS were developed by a European committee as part of the Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) initiative. These recommendations were published in the Annals of the Rheumatic Diseases in 2019. (1) The North American Childhood Arthritis and Rheumatology Research Alliance (CARRA) also developed separate consensus based treatment plans, which similarly emphasise the importance of methotrexate and corticosteroids in managing JLS. (6)

SCOPE

This guideline focuses on the diagnosis, assessment and management of localised scleroderma in children and young people (CYP), based on the consensus recommendations developed by the SHARE initiative. This guideline can be used by rheumatologists, dermatologists and all those involved in the care of CYP with JLS.

DIAGNOSIS AND ASSESSMENT

To ensure all CYP receive appropriate JLS management, all patients with JLS should be referred to a Paediatric Rheumatologist and ideally have shared care with Rheumatology and Dermatology. Disease activity and damage must be assessed at diagnosis and throughout follow up. Identifying and quantifying JLS activity allows clinicians to assess response to treatment. The LoSCAT (Localised Scleroderma Cutaneous Assessment Tool) is a validated scoring system that includes a Skin Severity Index (LoSSI) and a Skin Damage Index (LoSDI), does not require specialist equipment and can be used in daily practice. (7,8) See Appendix 1.

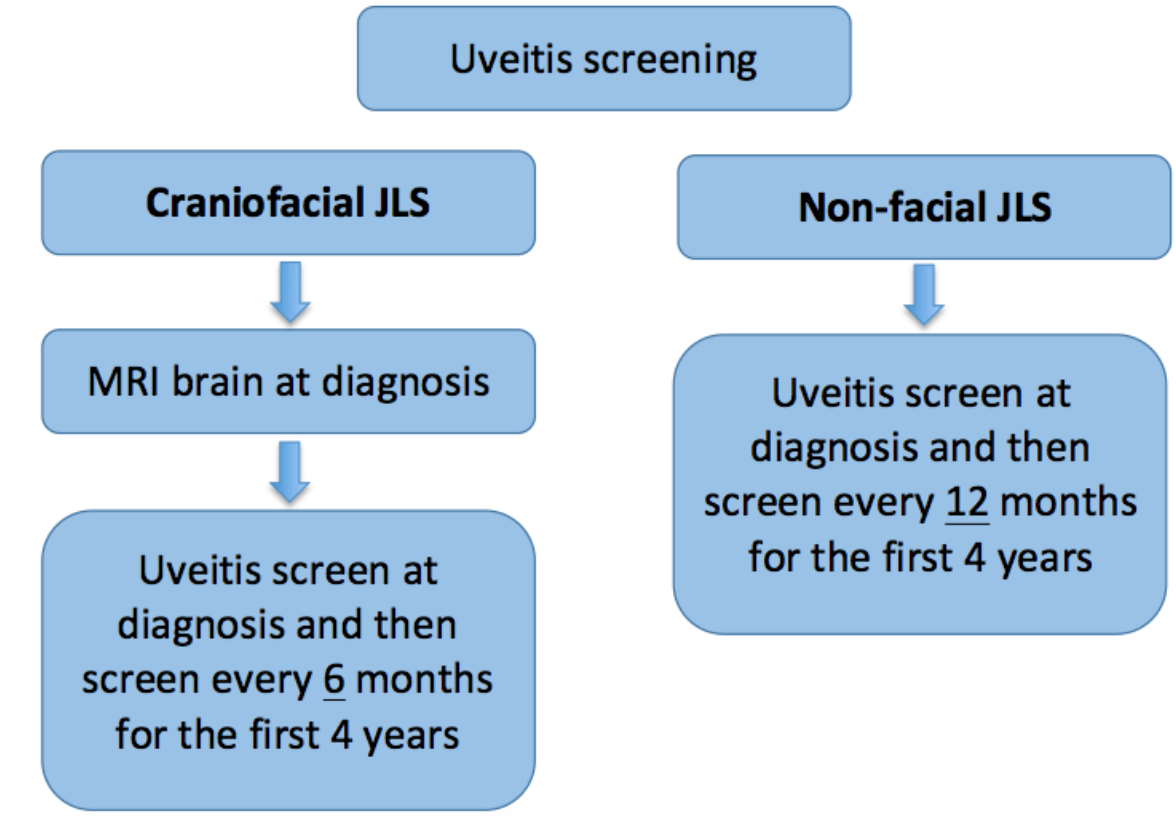
Medical Photography is an essential adjunct in these cases to allow photographic chronological documentation.
Non-invasive techniques such as high frequency ultrasound (9) and infrared thermography (IT) can be used to assess cutaneous involvement, but access to these tools in Scotland can be variable and in practice these are not used routinely. IT can also lead to false positive results due to increased induction of heat in old inactive lesions due to skin atrophy (10).

Up to 20% of CYP with JLS will have extracutaneous features such as arthritis, uveitis, other autoimmune conditions and central nervous system (CNS) involvement. Articular involvement is most common and can be present in any subtype of JLS. Therefore, all CYP should have a thorough joint examination including temporomandibular joint (TMJ) assessment and leg length measurement. (11) Studies in adults have also found MRI (with contrast) to be a useful tool in assessing for articular involvement. (12)
CNS involvement is rare, but more common in CYP with linear scleroderma of the face and scalp (craniofacial). They may present with headache, changes in behaviour and/or seizures and have a variety of abnormalities on MRI head. (11,13) Ocular involvement, either directly due to involvement of tissues in JLS lesions or asymptomatic uveitis, as well as orthodontic/maxillofacial involvement is also associated with craniofacial linear scleroderma. (14,15) These CYP should be considered for an MRI head at diagnosis as well as specialist assessment and follow up for extracutaneous features.

Key principles in diagnosis and assessment of JLS
Any CYP with suspected localised scleroderma should be referred to a specialised paediatric rheumatology centre
The LoSCAT tool should be used to assess disease activity and severity of JLS lesions (LoSSI tool) as well as to assess damage in JLS (LoSDI tool). This should be done at each visit.
Activity of JLS lesions can also be assessed by infrared thermography but a false-positive may result from skin atrophy
Activity of JLS lesions as well as extent and response to treatment can be assessed using standardised ultrasound imaging with colour Doppler
At diagnosis and throughout follow-up all CYP with JLS should have a detailed joint examination including TMJ
To assess musculoskeletal involvement in JLS, in particular where a lesion crosses a joint, MRI is a useful tool.
All CYP with craniofacial JLS (+/- CNS signs or symptoms) should have an MRI head at diagnosis
All CYP with craniofacial JLS should have orthodontic and maxillofacial assessment at diagnosis and throughout follow-up
All CYP with JLS, should have uveitis screening by ophthalmology at diagnosis and throughout follow up. The screening schedule will vary depending on whether the JLS is craniofacial or not.

UVEITIS SCREENING

The following uveitis screening flow chart is also supported by the minimum standards of care set out by the Paediatric Rheumatology European Society (PRES) Scleroderma Working Group in 2018. (16)



All CYP with JLS should be screened for extracutaneous features as appropriate

MANAGEMENT

Treatment strategies should be based on the subtype of JLS as well as the activity and site of the lesions. In all but small, solitary, superficial lesions, systemic treatment is warranted.

STEROIDS

Systemic corticosteroids are used widely in the management of the active phase of JLS, often in combination with disease-modifying antirheumatic drugs (DMARD). They are effective but there is no clear consensus on dose and administration route. There are two main regimens of:

- Oral prednisolone of 1-2 mg/kg/day over 2-3 months with tapering protocol following, or
- Intravenous methylprednisolone 30 mg/kg of varying schedules. (17,18)

The generally accepted steroid schedule in Scotland is 3 days of IV methylprednisolone 30 mg/kg followed by single monthly doses for a total of 6 months. Steroid regimen is at the clinician's discretion. Please consider the need for short synacthen test and sick day dosing on a case-by-case basis according to local protocols.

METHOTREXATE

All patients with active JLS should be treated with a DMARD. Methotrexate (MTX) has been shown in a randomised controlled trial by Zulian et al to be highly effective and generally well tolerated. (19) Patients would typically be prescribed systemic corticosteroids alongside MTX as a 'bridge therapy'. The recommended weekly dose of MTX is 15 mg/m2 as single weekly oral or subcutaneous dose and should continue for at least 12 months following clinical remission before tapering. (18)

MYCOPHENOLATE MOFETIL

For patients with severe / refractory JLS or who are MTX-intolerant, mycophenolate mofetil (MMF) can be used at a dose of 500-1000 mg/m2. The most commonly used MMF dosing regimen in Scotland is 600 mg/m2 twice daily and patients will titrate up to this dose. MMF has been demonstrated to be an effective second line agent (either instead of / in addition to MTX) in case series and retrospective studies. (20-22)

TOPICAL TREATMENT

Topical treatment is recommended for isolated circumscribed superficial lesions. Imiquimod 5% cream has been proven to decrease skin thickening. (23) However, due to the lack of paediatric data, further research for its use in JLS has been recommended by the SHARE initiative (1). Moderate to high potency topical corticosteroids are also used but there are no clinical studies that demonstrate benefit. (24) Studies of Vitamin D derivatives, such as Calcipotriol, with phototherapy as well as topical Tacrolimus 0.1% have demonstrated significant improvement in skin softening. (24-26)

PHOTOTHERAPY

Phototherapy with medium-dose ultraviolet light A1 can also be used to increase skin softness in isolated circumscribed lesions but also has limited evidence for its use. (27) The increased risks of carcinogenesis and skin ageing due to the need for protracted maintenance therapy in CYP with JLS should be considered. (28)

BIOLOGICS

There have been many case series and small number studies regarding alternative agents for refractory / severe JLS. Abatacept and Tocilizumab are the most common biologics described, are generally well tolerated and result in improved symptoms and JLS activity scores. (29-33) They should be considered at the clinician's

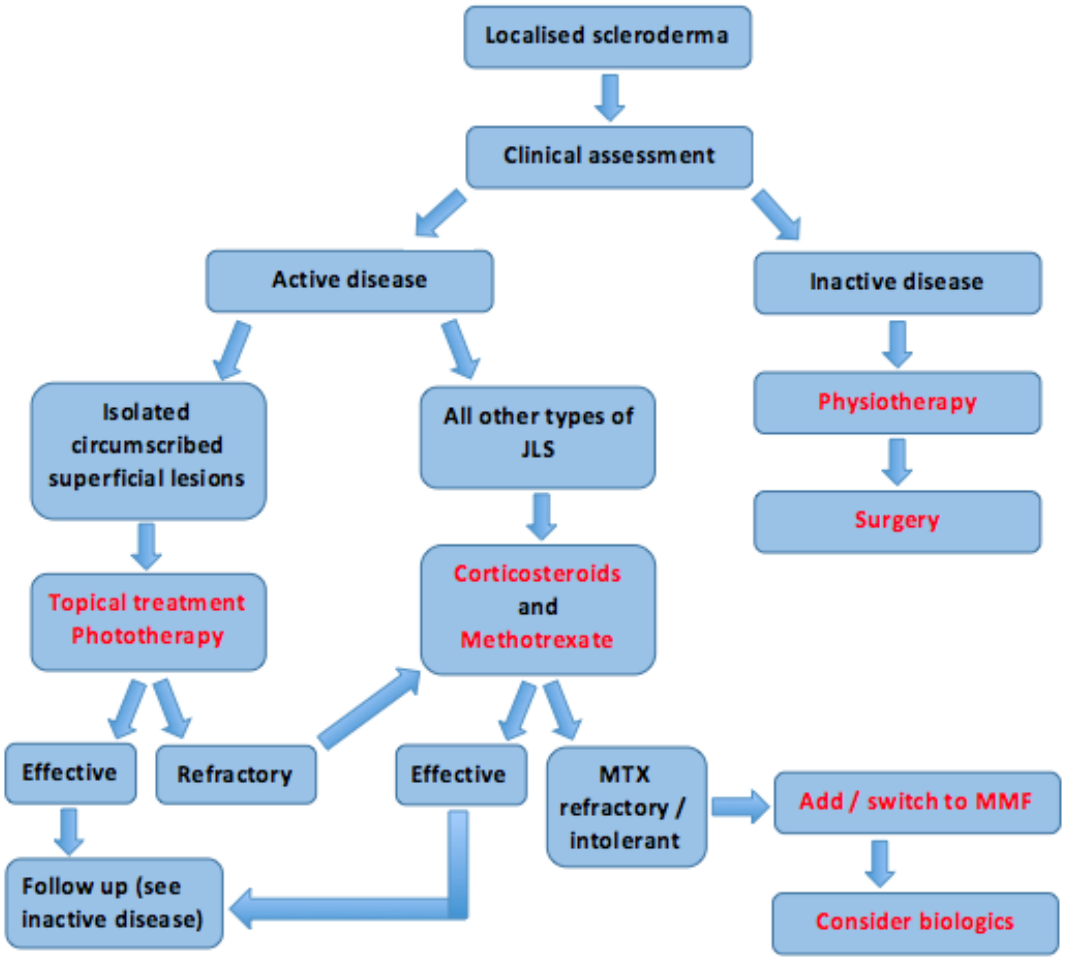
discretion. There are case reports of a number of other agents including hydroxychloroquine, ciclosporin, azathioprine, retinoids, IV immunoglobulin, rituximab, infliximab and janus kinase inhibitors being used in isolation or in addition to other standard therapies. However there is currently not enough evidence to advise their use.

PHYSIOTHERAPY AND OCCUPATIONAL THERAPY

Physical and occupational therapy is recommended for all patients with restricted joint movement / muscle weakness in conjunction with topical / systemic management. (1)

OTHER

In a small number of patients, surgery for leg lengthening or fat transfer may be required. These cases should be assessed and discussed with local specialists (orthopaedics or plastic surgeons) on a case-by-case basis. (24, 34)
This flowchart for management of JLS is adapted from the SHARE initiative.



REFERENCES

1. Zulian F, Culpo R, Sperotto F, Anton J, Avcin T, Baildam EM, Boros C, Chaitow J, Constantin T, Kasapcopur O, Knupp Feitosa de Oliveira S, Pilkington CA, Russo R, Toplak N, van Royen A, Saad Magalhães C, Vastert SJ, Wulffraat NM, Foeldvari I. Consensus-based recommendations for the management of juvenile localised scleroderma. Ann Rheum Dis. 2019 Aug;78(8):1019-1024. doi: 10.1136/annrheumdis-2018-214697.

2. Laxer RM, Zulian F. Localized scleroderma. Curr Opin Rheumatol. 2006 Nov;18(6):606-13. doi: 10.1097/01.bor.0000245727.40630.c3.

3. Herrick AL, Ennis H, Bhushan M, Silman AJ, Baildam EM. Incidence of childhood linear scleroderma and systemic sclerosis in the UK and Ireland. Arthritis Care Res (Hoboken). 2010 Feb;62(2):213-8. doi: 10.1002/acr.20070.

4. Zulian F, Athreya BH, Laxer R, Nelson AM, Feitosa de Oliveira SK, Punaro MG, Cuttica R, Higgins GC, Van Suijlekom-Smit LW, Moore TL, Lindsley C, Garcia-Consuegra J, Esteves Hilário MO, Lepore L, Silva CA, Machado C, Garay SM, Uziel Y, Martini G, Foeldvari I, Peserico A, Woo P, Harper J; Juvenile Scleroderma Working Group of the Pediatric Rheumatology European Society (PRES). Juvenile localized scleroderma: clinical and epidemiological features in 750 children. An international study. Rheumatology (Oxford). 2006 May;45(5):614-20. doi: 10.1093/rheumatology/kei251.

5. Zulian F, Vallongo C, de Oliveira SK, Punaro MG, Ros J, Mazur-Zielinska H, Galea P, Da Dalt L, Eichenfield LF. Congenital localized scleroderma. J Pediatr. 2006 Aug;149(2):248-51. doi: 10.1016/j.jpeds.2006.04.052.

6. Li SC, Torok KS, Pope E, Dedeoglu F, Hong S, Jacobe HT, Rabinovich CE, Laxer RM, Higgins GC, Ferguson PJ, Lasky A, Baszis K, Becker M, Campillo S, Cartwright V, Cidon M, Inman CJ, Jerath R, O'Neil KM, Vora S, Zeft A, Wallace CA, Ilowite NT, Fuhlbrigge RC; Childhood Arthritis and Rheumatology Research Alliance (CARRA) Localized Scleroderma Workgroup. Development of consensus treatment plans for juvenile localized scleroderma: a roadmap toward comparative effectiveness studies in juvenile localized scleroderma. Arthritis Care Res (Hoboken). 2012 Aug;64(8):1175-85. doi: 10.1002/acr.21687.

7. Arkachaisri T, Vilaiyuk S, Li S, O'Neil KM, Pope E, Higgins GC, Punaro M, Rabinovich EC, Rosenkranz M, Kietz DA, Rosen P, Spalding SJ, Hennon TR, Torok KS, Cassidy E, Medsger TA Jr; Localized Scleroderma Clinical and Ultrasound Study Group. The localized scleroderma skin severity index and physician global assessment of disease activity: a work in progress toward development of localized scleroderma outcome measures. J Rheumatol. 2009 Dec;36(12):2819-29. doi: 10.3899/jrheum.081284.

8. Arkachaisri T, Vilaiyuk S, Torok KS, Medsger TA 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 Feb;49(2):373-81. doi: 10.1093/rheumatology/kep361.

9. Li SC, Liebling MS, Haines KA. Ultrasonography is a sensitive tool for monitoring localized scleroderma. Rheumatology (Oxford). 2007 Aug;46(8):1316-9. doi: 10.1093/rheumatology/kem120. Epub 2007 May 27. PMID: 17526926.

10. Martini G, Murray KJ, Howell KJ, Harper J, Atherton D, Woo P, Zulian F, Black CM. Juvenile-onset localized scleroderma activity detection by infrared thermography. Rheumatology (Oxford). 2002 Oct;41(10):1178-82. doi: 10.1093/rheumatology/41.10.1178.

11. Zulian F, Vallongo C, Woo P, Russo R, Ruperto N, Harper J, Espada G, Corona F, Mukamel M, Vesely R, Musiej-Nowakowska E, Chaitow J, Ros J, Apaz MT, Gerloni V, Mazur-Zielinska H, Nielsen S, Ullman S, Horneff G, Wouters C, Martini G, Cimaz R, Laxer R, Athreya BH; Juvenile Scleroderma Working Group of the Pediatric Rheumatology European Society (PRES). Localized scleroderma in childhood is not just a skin disease. Arthritis Rheum. 2005 Sep;52(9):2873-81. doi: 10.1002/art.21264.

12. Schanz S, Fierlbeck G, Ulmer A, et al.. Localized scleroderma: MR findings and clinical features. Radiology 2011 Sep;260:817–24. doi: 10.1148/radiol.11102136

13. Blaszczyk M, Królicki L, Krasu M, Glinska O, Jablonska S. Progressive facial hemiatrophy: central nervous system involvement and relationship with scleroderma en coup de sabre. J Rheumatol. 2003 Sep;30(9):1997-2004. PMID: 12966605.

14. Zannin ME, Martini G, Athreya BH, Russo R, Higgins G, Vittadello F, Alpigiani MG, Alessio M, Paradisi M, Woo P, Zulian F; Juvenile Scleroderma Working Group of the Pediatric Rheumatology European Society (PRES). Ocular involvement in children with localised scleroderma: a multi-centre study. Br J Ophthalmol. 2007 Oct;91(10):1311-4. doi: 10.1136/bjo.2007.116038.

15. Trainito S, Favero L, Martini G, Pedersen TK, Favero V, Herlin T, Zulian F. Odontostomatologic involvement in juvenile localised scleroderma of the face. J Paediatr Child Health. 2012 Jul;48(7):572-6. doi: 10.1111/j.1440-1754.2012.02435.x.

16. Constantin T, Foeldvari I, Pain CE, Pálinkás A, Höger P, Moll M, Nemkova D, Weibel L, Laczkovszki M, Clements P, Torok KS. Development of minimum standards of care for juvenile localized scleroderma. Eur J Pediatr. 2018 Jul;177(7):961-977. doi: 10.1007/s00431-018-3144-8.

17. Uziel Y, Feldman BM, Krafchik BR, Yeung RS, Laxer RM. Methotrexate and corticosteroid therapy for pediatric localized scleroderma. J Pediatr. 2000 Jan;136(1):91-5. doi: 10.1016/s0022-3476(00)90056-8.

18. Weibel L, Sampaio MC, Visentin MT, Howell KJ, Woo P, Harper JI. Evaluation of methotrexate and corticosteroids for the treatment of localized scleroderma

(morphoea) in children. Br J Dermatol. 2006 Nov;155(5):1013-20. doi: 10.1111/j.1365-2133.2006.07497.x.

19. Zulian F, Martini G, Vallongo C, Vittadello F, Falcini F, Patrizi A, Alessio M, La Torre F, Podda RA, Gerloni V, Cutrone M, Belloni-Fortina A, Paradisi M, Martino S, Perilongo G. Methotrexate treatment in juvenile localized scleroderma: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2011 Jul;63(7):1998-2006. doi: 10.1002/art.30264.

20. Martini G, Ramanan AV, Falcini F, Girschick H, Goldsmith DP, Zulian F. Successful treatment of severe or methotrexate-resistant juvenile localized scleroderma with mycophenolate mofetil. Rheumatology (Oxford). 2009 Nov;48(11):1410-3. doi: 10.1093/rheumatology/kep244.

21. Kaushik A, Mahajan R, De D, Handa S. Paediatric morphoea: a holistic review. Part 2: diagnosis, measures of disease activity, management and natural history. Clin Exp Dermatol. 2020 Aug;45(6):679-684. doi: 10.1111/ced.14236.

22. Martini G, Saggioro L, Culpo R, Vittadello F, Meneghel A, Zulian F. Mycophenolate mofetil for methotrexate-resistant juvenile localized scleroderma. Rheumatology (Oxford). 2021 Mar 2;60(3):1387-1391. doi: 10.1093/rheumatology/keaa392.

23. Dytoc M, Ting PT, Man J, Sawyer D, Fiorillo L. First case series on the use of imiquimod for morphoea. Br J Dermatol. 2005 Oct;153(4):815-20. doi: 10.1111/j.1365-2133.2005.06776.x.

24. Li SC, Zheng RJ. Overview of Juvenile localized scleroderma and its management. World J Pediatr. 2020 Feb;16(1):5-18. doi: 10.1007/s12519-019-00320-9.

25. Kreuter A, Gambichler T, Avermaete A, Jansen T, Hoffmann M, Hoffmann K, Altmeyer P, von Kobyletzki G, Bacharach-Buhles M. Combined treatment with calcipotriol ointment and low-dose ultraviolet A1 phototherapy in childhood morphea. Pediatr Dermatol. 2001 May-Jun;18(3):241-5. doi: 10.1046/j.1525-1470.2001.018003241.x.

26. Kroft EB, Groeneveld TJ, Seyger MM, de Jong EM. Efficacy of topical tacrolimus 0.1% in active plaque morphea: randomized, double-blind, emollient-controlled pilot study. Am J Clin Dermatol. 2009;10(3):181-7. doi: 10.2165/00128071-200910030-00004.

27. Su O, Onsun N, Onay HK, Erdemoglu Y, Ozkaya DB, Cebeci F, Somay A. Effectiveness of medium-dose ultraviolet A1 phototherapy in localized scleroderma. Int J Dermatol. 2011 Aug;50(8):1006-13. doi: 10.1111/j.1365-4632.2010.04843.x.

28. Staberg B, Wulf HC, Klemp P, Poulsen T, Brodthagen H. The carcinogenic effect of UVA irradiation. J Invest Dermatol. 1983 Dec;81(6):517-9. doi: 10.1111/1523-1747.ep12522855.

29. Li SC, Torok KS, Ishaq SS, Buckley M, Edelheit B, Ede KC, Liu C, Rabinovich CE. Preliminary evidence on abatacept safety and efficacy in refractory juvenile localized scleroderma. Rheumatology (Oxford). 2021 Aug 2;60(8):3817-3825. doi: 10.1093/rheumatology/keaa873

30. Kalampokis I, Yi BY, Smidt AC. Abatacept in the treatment of localized scleroderma: A pediatric case series and systematic literature review. Semin Arthritis Rheum. 2020 Aug;50(4):645-656. doi: 10.1016/j.semarthrit.2020.03.020.

31. Lythgoe H, Baildam E, Beresford MW, Cleary G, McCann LJ, Pain CE. Tocilizumab as a potential therapeutic option for children with severe, refractory juvenile localized scleroderma. Rheumatology (Oxford). 2018 Feb 1;57(2):398-401. doi: 10.1093/rheumatology/kex382.

32. Martini G, Campus S, Raffeiner B, Boscarol G, Meneghel A, Zulian F. Tocilizumab in two children with pansclerotic morphoea: a hopeful therapy for refractory cases? Clin Exp Rheumatol. 2017 Sep-Oct;35 Suppl 106(4):211-213. Epub 2017 Sep 29. PMID: 28980909.

33. Osminina M, Geppe N, Afonina E. Scleroderma "en coup de sabre" With Epilepsy and Uveitis Successfully Treated With Tocilizumab. Reumatol Clin (Engl Ed). 2020 Sep-Oct;16(5 Pt 1):356-358. English, Spanish. doi: 10.1016/j.reuma.2018.05.001

34. Kreuter A, Krieg T, Worm M, Wenzel J, Moinzadeh P, Kuhn A, Aberer E, Scharffetter-Kochanek K, Horneff G, Reil E, Weberschock T, Hunzelmann N. German guidelines for the diagnosis and therapy of localized scleroderma. J Dtsch Dermatol Ges. 2016 Feb;14(2):199-216. doi: 10.1111/ddg.12724