Tocilizumab in two children with pansclerotic morphoea: a hopeful therapy for refractory cases?

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ABSTRACT

Pansclerotic morphoea (PM) is a subtype of juvenile localised scleroderma characterised by severe course with generalised full-thickness skin involvement and possible growth and functional impairment. PM treatment comprises a combination of immunosuppressive agents such as corticosteroids, methotrexate, mycophenolate mofetil, PUVA and antithymocyte globulin and biological agents used in off-label. A possible role of IL-6 in the regulation of fibroblast differentiation and stimulation of collagen synthesis has been suggested and in patients with systemic sclerosis (SSc) the treatment with tocilizumab (TCZ) was associated to improvement of skin thickness and joint motion. We describe the first two cases of children with PM refractory to different immunosuppressive agents in which the use of TCZ reduced disease activity and stopped disease progression. Therefore, we suggest that an earlier use of this agent in such severe cases could be considered before irreversible sclerosis and tissue damage occurs.

Juvenile localised scleroderma (JLS) comprises a group of autoimmune fibrosing conditions involving skin and subcutaneous tissues following an initial inflammatory reaction. Pansclerotic morphoea (PM), an extremely rare and severe subtype of JLS, is characterised by generalised full-thickness skin involvement that may extend over deeper tissues and bone with subsequent growth disturbance and disabling outcome. We describe the first two children with PM refractory to immunosuppressive treatments in which the off-label use of tocilizumab (TCZ), fully humanised anti IL-6R antibody, allowed to control the inflammation and stopped the extension of the disease.

Case reports

Patient 1 is a 16-year-old girl affected by JLS mixed subtype (PM on right limb and deep morphoea on trunk) since the age of 4. Diagnosis was made 18 months after onset and prednisone (PDN) 2 mg/kg/day and methotrexate (MTX) 15 mg/m2/week were started. Nine months later, because of persistent activity, we administered 3 pulses of methylprednisolone (MPDN 30 mg/kg each) and added mycophenolate mofetil (MMF) 700 mg/m^2/day. In the following two years improvement was observed on clinical and thermographic evaluations so PDN was slowly tapered and MMF reduced. After being lost to follow-up for months, patient presented new lesions on abdomen and worsening of fibrosis on right limb. She refused MTX and MMF so imatinib 200 mg/day was started but, in the following 4 years, severity of tissue atrophy dramatically progressed with marked leg growth impairment and persistent activity on back, shoulders, neck and left thigh (Fig. 1). Disease activity and damage index LoSCAT was 58 (mLoSSI 15, LoSDI 43) (1) so we started TCZ 8 mg/kg every 4 weeks with rapid reduction of inflammation since first infusions (Fig. 2). Eighteen months later, treatment is still ongoing, lesions are inactive and leg atrophy is stable (LoSCAT 47, mLoSSI 7, LoSDI 40). Patient tolerated treatment well, except for an episode of pneumonia treated with oral antibiotics.

Patient 2 at 4 years progressively developed diffuse thickening of trunk, buttocks and lower limbs. We saw him six months after onset and found mRodnan skin score 21 with hip and knees limitation and significant hyperthermia on thermography. He was started on MTX 15 mg/m^2/weekly and PDN 2 mg/kg/day and in following

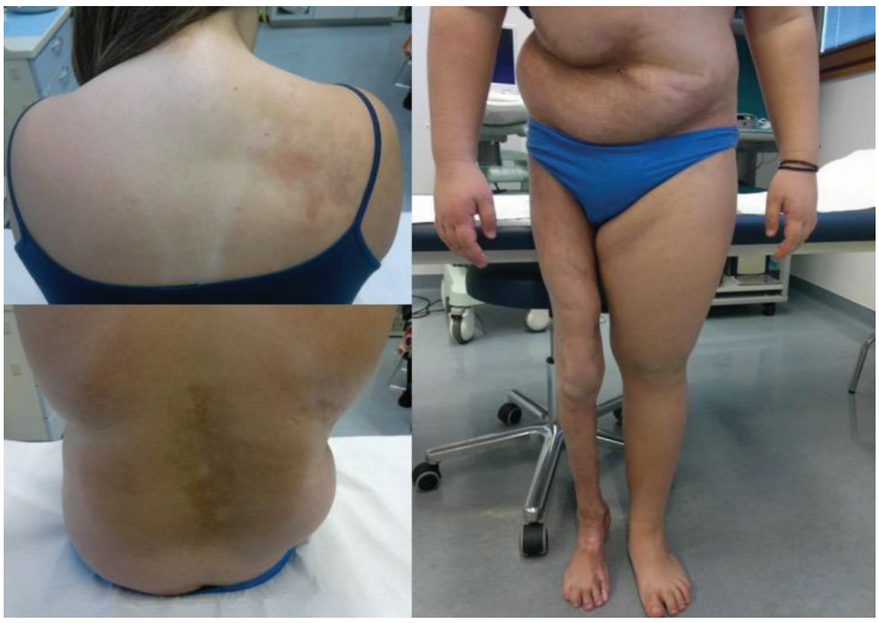

Fig. 1. Patient no. 1 scleroderma lesions with signs of activity (hyperaemia, skin thickening) on the back, the right shoulder and the left thigh. Note the marked atrophy of the whole right lower limb.

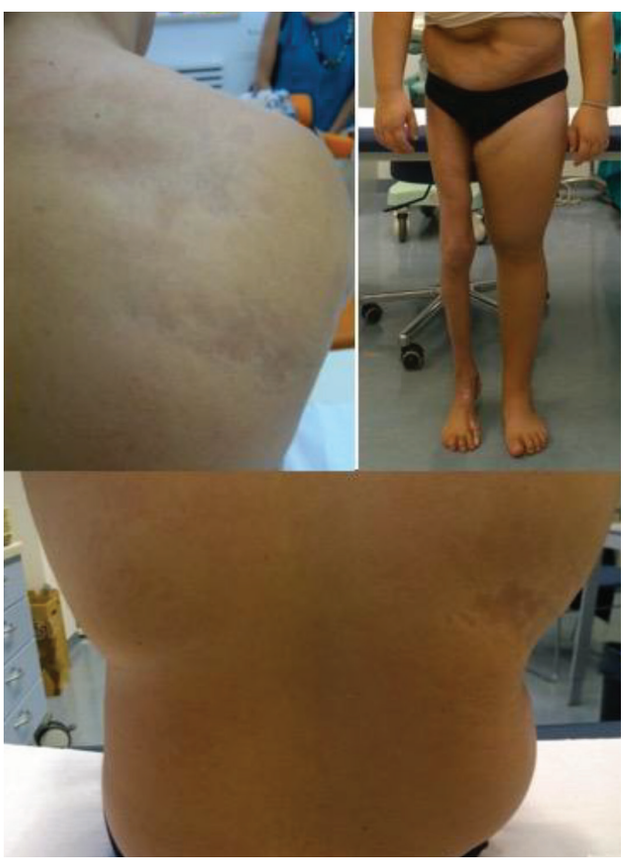

Fig. 2. Patient no.1 improvement of the lesions 6 months after TCZ treatment start.

six months, skin softened (mRodnan 8) and hyperthermia on thermography decreased. Fifteen months later, after PDN reduction, new lesions appeared so we added MMF 700 mg/m^2/day. In following 3 years, lesions improved so PDN was gradually withdrawn as well as the dose of MMF and MTX but 2 months later, lesions on lateral aspect of thighs extended with worsening of thickness and erythema and limitation of knees (mRodnan 14, LoSCAT 57, mLoSSI 24, LoSDI 33). Lesions persisted active despite steroids (3 monthly MPDN pulses and PDN), MMF 700 mg/m2/day and MTX 10 mg/m2/week. Therefore, after 6 months, we started TCZ 8 mg/kg every 4 weeks. TCZ was well tolerated, no new lesion appeared and an improvement of lesion activity both by clinical (reduction of skin erythema and thickening) and thermographic parameters was observed (Fig. 2a and 2b). We performed 6 monthly infusions of TCZ with sustained improvement allowing withdraw PDN and reduce MTX and MMF doses. Twenty-four months from last infusion lesions are still inactive both by clinical and thermography evaluation (mRodnan 6, LoSCAT 43, mLoSSI 10, LoSDI 33) (Fig. 2c and d).

Discussion

PM represents 2% of LS cases and is certainly the most severe subtype characterised by full-thickness induration of the skin and underlying tissues that usually involve trunk, extremities, face and scalp with sparing of fingertips and toes and absence of Raynaud's phenomenon (2). As other subtypes of localised scleroderma, PM is far more frequent in children although some cases have been reported in adulthood (3). Recent reports raised the attention on the possible evolution of deep trophic ulcers, frequently complicating longstanding PM, to squamous cell carcinoma a threatening complication already reported in SSc (3, 4). Moreover, in PM the tissue atrophy is responsible for the development of disabling deformities of the affected limbs with severe functional and vascular impairment that can lead to limb amputation. The treatment of JLS is challenging and given the rarity of the disease and the absence of agreed and validated outcome measures there have been only few therapeutic trials. In general, first line therapy is a combination of methotrexate with corticosteroids as supported by a randomised placebo controlled trial in which all children were treated with oral PDN for 3 months and either received oral MTX 15mg/m^2 or placebo (5). In this study, a disease relapse occurred in only 32.6%

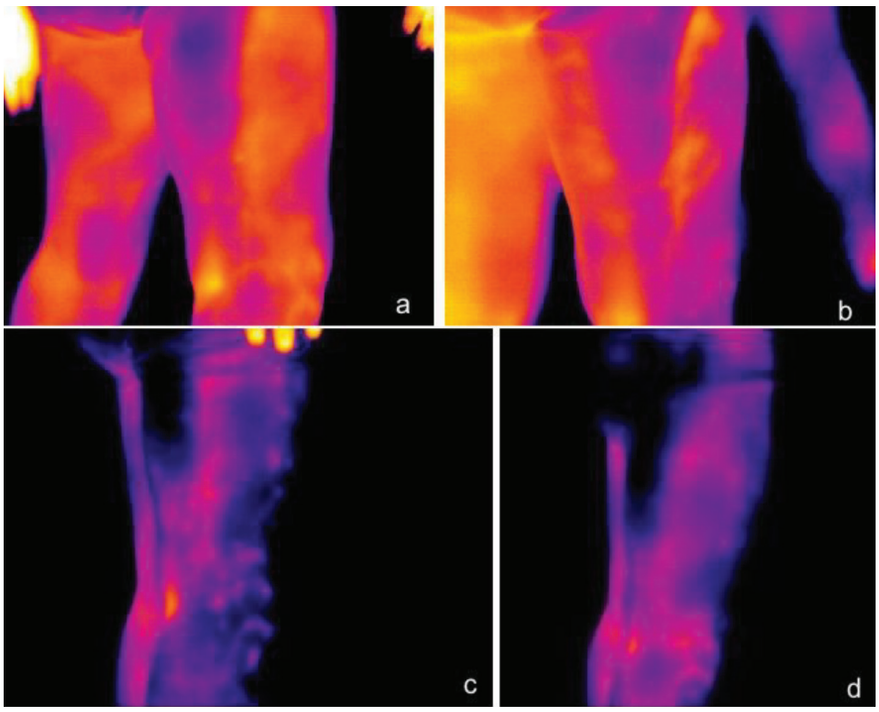

Fig. 3. Patient no. 2 infrared thermography examination of scleroderma lesion on the right thigh showing marked hyperthermia before TCZ treatment (a) and progressive improvement after 2 and 6 infusions (b and c, respectively) and at last evaluation 18 months after last infusion (d).

of the MTX group *versus* 70.8% in the placebo group (p<0.005). In refractory cases MMF can be effective, as showed in a case series, and the use of other immunosuppressive drugs alone or in combination with PUVA, antithymocyte globulin and biological agents as off-label have been reported in various small pilot series (6-10). The rationale for using TCZ in our patients derived from some observation of a possible role of IL-6, a pro-inflammatory cytokine, in the pathophysiology of LS by regulating fibroblast differentiation and stimulating collagen synthesis (11, 12). Moreover, IL-6 has been detected in serum of patients with LS and its levels appear to reduce in parallel with improvement of disease activity parameters (13). In patients with systemic sclerosis (SSc) the treatment with TCZ both by IV infusions and subcutaneously lead to improvement of skin thickness and joint motion and to significant thinning of the collagen fibre bundles in the dermis and reduction of number of αSMA-positive myofibroblasts that have been reported to exhibit abundant production of collagen (14, 15). In our experience TCZ was effective in reducing disease activity in both treated patients which had long-standing and resistant PM with severe irreversible tissue damage; therefore, we suggest that this agent could be used earlier in such severe cases before extensive sclerosing tissue damage occurs. Although limited in being a small case series, this report suggests that TCZ can be effective in patients with PM so further and larger studies are needed to confirm these preliminary results.

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