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Morphea – selected local treatment methods and their effectiveness

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Abstract

Localised scleroderma is an uncommon connective tissue disease of multifactorial aetiology occurring in the paediatric and adult population. It is relatively difficult to conduct any research on the subject of this disease entity treatment due to the low number of patients suffering from morphea, a tendency of the disease to remit spontaneously, and not yet well recognised aetiology. Hence, there has been developed no causal treatment of well-proven effectiveness, and schedules of symptomatic therapy are not yet clearly determined. The paper depicts most widely used topical treatment methods in morphea therapy, which due to minor risk of systemic adverse effects seem to be a beneficial therapeutic alternative. The main aim of this article was to analyse different topical treatment options used in localised scleroderma therapy and to indicate the most appropriate, safe, and effective one.

Key words: systematic review, topical treatment, localised scleroderma.

Introduction

Localised scleroderma is a relatively rare connective tissue disease occurring not only in adults, but also in child patients. The aetiology of morphea is not yet well recognised, but its multifactorial character seems obvious. It is highly possible that a major part in morphea pathogenesis is played by endothelial cell damage, which can be a factor initiating the disease process. Damage may be caused among others by traumas, infections, hypoxia, antiendothelial cell autoantibodies (AECA), or reactive oxygen species. The consequence of this process is an increased expression of adhesion molecules, activation of T and B lymphocytes, enhanced production of proinflammatory cytokines and profibrotic growth factors, macrophages, and eosinophils activation [1, 2].

Among the above-mentioned mediators stimulating fibrosis process, interleukin 4, 6, 8 (IL-4, IL-6, IL-8), transforming growth factor β (TGF-β), platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF), and insulin-like growth factor (IGF) [3, 4] are of significance. The increased levels of various cytokines, such as IFN-γ-inducible protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), interleukin 17α (IL-17α), interleukin 12p70 (IL-12p70), interferon α2 (IFN-α2), and interferon γ (IFN-γ) [5], is also noticed among the patients. The results of the processes mentioned earlier are an increased synthesis and deposition in the dermis of collagen (particularly subtype I and III), proteoglycans and fibronectin, and decreased production of metalloproteinase extracellular matrix (MMP), which lead to fibrosis and indurations of the skin. Activation of antigen presenting cells can also contribute to additional autoantibody synthesis [2].

Genetic and epigenetic susceptibility is also taken into consideration in the pathogenesis of the disease. It has been determined that the presence of human leukocyte antigens HLA-DRB1*04:04, HLA-B*37, HLA-DR5, DR8, and DR11 is connected with a higher risk of morphea occurrence. At the same time, family occurrence is

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very rare. More often different autoimmune or rheumatic diseases are diagnosed not only in the patient, but also in a family history. The frequency of such coincidence amounts to 46% [6, 7]. The clinical manifestation of localised scleroderma is highly diversified and depends on the disease subtype, localisation of the changes, and the depth of involvement. According to the classification created by Laxer and Zulian, we can differentiate five varying types of morphea: pansclerotic, linear, circumscribed, generalised, and mixed [2]. The disease process may include only skin, but it can also extend to deeper situated tissues, such as fascia, muscle, and even bone. Morphea of severe course is a potential cause of deformations and impairment of mobility joint contracture, leading to permanent disability. For that reason, it is of utmost importance to enable suitable treatment as fast as possible.

The paper depicts the most widely used therapy topical treatment methods in morphea, but it must be mentioned that topical treatment may not be sufficient in every case, and its application should be limited mainly to the therapy of non-progressive superficial lesions. Having diagnosed a morphea characterised by rapid progression of skin changes, it may be necessary to apply systemic therapy, e.g. morphea profunda requires systemic corticosteroids and methotrexate as the first-line treatment. Therefore, in every case, before enabling treatment factors such as disease subtype and activity, the depth of involvement and the extent to which the changes impair the person's quality of life should be taken into consideration [8].

Topical and intralesional corticosteroid therapy

Source literature does not currently comprise any credible research confirming the hypothesis of high efficacy of treatment with locally applied corticosteroids, both topically and intralesionally. However, a few cases were described, where local application of corticosteroids in combination with calcipotriol was proved to be effective [9]. Even though there were no unambiguous evidence proving the effectiveness of such treatment, local application of corticosteroids is still recommended in cases with superficial lesions in the active phase of the disease [10, 11].

The main objective of such proceedings is to diminish the inflammation and inhibit further progression of the disease. Corticosteroid preparation can also be put under occlusion to increase its potency. German guidelines for treating localised scleroderma recommend using highly potent steroids for a duration of one month or moderately potent for a duration of three months. In both schedules of treatment corticosteroids should be applied on the lesion once every day [11]. Similar durations of therapy are recommended by different authors [3, 12].

Having taken into consideration the risk of adverse effects that can appear when treating with locally applied corticosteroids, in the case of a longer duration of treatment interval therapy should be performed. Practicing local treatment with corticosteroids seems to be relatively safe even for pregnant women, but it has been proven that an external therapy with potent and very potent topical corticosteroids may increase the risk of foetal growth restriction occurrence. However, there is no risk of such side effects using low-potency or moderate-potency corticosteroids [13, 14]. As has been already mentioned, there is no research proving the effectiveness of corticosteroids applied directly into the lesion, but it may prove beneficial in the case of linear scleroderma type en coup de sabre in active stage. An injection is to be given on the edge of the lesion once a week for a duration of three weeks [3, 7, 11].

Calcineurin inhibitors (topical tacrolimus)

Among the most widely used in dermatology calcineurin, tacrolimus, and pimecrolimus inhibitors, only the effectiveness of tacrolimus therapy in treating morphea has been examined until now. In a randomised, double-blind, petrolatum-controlled pilot study the high efficacy of localised scleroderma topical treatment using tacrolimus 0.1% ointment has been confirmed. During this therapy, the preparation was applied twice a day with no occlusion for a duration of 12 weeks [15].

In the other research, such treatment was practiced for a duration of four months. The therapy resulted in a better response to the performed treatment in the areas of early erythematous lesion that are characterised by an intensified inflammatory component comparing to longer-lasting and well-established thicker lesions. In the areas where lesions have yielded no hypo- or hyperpigmentation was observed and no notice of disease recurrence was taken within one year after finishing the therapy for patients with good response to the treatment [16].

In cases of the abovementioned studies, no significant side effects were noticed during the therapy. A case study published in source literature indicates high effectiveness and relative safety of therapies based on locally applied calcineurin inhibitors in treating localised scleroderma [17]. Significant improvement in the area of late lesions and full recovery in the area of new lesions was noticed during the treatment with tacrolimus applied under occlusion twice a day at night [18]. Apart from well-known and common side effects of calcineurin inhibitors,

such as pruritus, burning, or erythema in the place of application, a possibility of different and rare side effects like dermatophyte infection, that was also reviewed in source literature, should be taken into consideration. It is not advised to use tacrolimus in the therapy of people with post-irradiation morphea, because of a higher risk of radiation-recalled dermatitis occurrence [8, 19, 20].

Topical vitamin D analogues

Source literature provides presently a few unrelated studies proving the effectiveness of using topical vitamin D analogues in localised scleroderma therapy. In an open-label clinic research, lasting three months and conducted on a group of 12 patients resistant to previous treatment with highly potent corticosteroids and in many cases also refractory to systemic therapy, a significant improvement was observed after application of calcipotriol 0.005% ointment applied on lesions twice a day (under occlusion at night). The therapy resulted in a considerable reduction of erythema, dyspigmentation, telangiectasis, and induration. No side effects were noticed. The efficacy of treatment using occlusion, which improves the absorption of calcipotriol, was proved to be much higher [21]. Case studies reviewed in source literature also confirm high effectiveness of vitamin D analogues both used in monotherapy and in combination with locally applied corticosteroids [8, 22, 23].

Relatively good results of vitamin D analogues topical therapy in combination with phototherapy were obtained using low-dose ultraviolet A1 (a cumulative dose of 800 J/cm^2) and calcipotriol 0.005% ointment applied twice a day. Having finished the treatment there was observed a considerable level of recovery among all the patients treated with the provided therapy, and no significant adverse reactions took place [24]. Positive results were also acquired in the case of treating linear scleroderma type en coup de sabre of severe course as a result of a combined PUVA therapy (a cumulative dose of 70 J/cm^2) and calcipotriol ointment applied on lesions twice a day [25]. It seems that a topical therapy based on vitamin D analogues can be successful in the case of superficial lesions, but there is a need to conduct a randomised, placebo-controlled trial to prove the beneficial effects of such treatment in the case of patients with morphea.

Topical imiquimod

Imiquimod is a topical immune response modifier stimulating synthesis of many cytokines, IFN-α and IFN-γ among them, that inhibit the production of collagen [26]. Source literature gives examples of miscellaneous prospective and case studies of localised scleroderma effective treatment. Topical treatment with imiquimod applied once a day for five subsequent days in a week and a therapy lasting four months resulted in a complete remission of the disease in two patients, and there was also observed a significant improvement of clinical and dermoscopic assessment in 12 patients treated once a day three days a week for six months [27, 28].

Conducted prospective studies on a paediatric population and adult patients proved the efficacy of imiquimod in plaque-type morphea therapy. In a placebo-controlled study performed on a group of adults external imiquimod therapy resulted in a significant improvement of skin changes – the reduction in DIET scoring (assessment of dyspigmentation, induration, erythema, and telangiectasis intensity) and considerable recovery in a histological view. No significant difference was observed in dermal and hypo-dermal thickness examined with ultrasound test. No systemic adverse reactions were noticed, but local side effects occurred, such as hypopigmented macules, ulcerations, and irritations, in 24% of patients [29]. In another study conducted on a paediatric population (of the average age of 11 years at the beginning of the trial) after 36 weeks of the therapy it was noticed that in the case of nine children there was a significant reduction in VAS (visual analogue scale) and DIET scoring. Moreover, an ultrasound test proved a decrease of dermal thickness. In the case of one patient it was necessary to terminate the therapy earlier, because of ulceration occurring in the place of medicine application [30]. Despite promising results and favourable safety profile, the authors of German guidelines [10] do not advise using imiquimod externally in treating localised scleroderma, on the basis of their own observations.

Intralesional interferon γ

Despite the potential fibrosis-suppressing effect of interferon γ (IFN-γ) in localised scleroderma therapy, randomised placebo-controlled research did not prove the effectiveness of such treatment [31].

Phototherapy

Phototherapy is one of the topical treatment methods that is best medically demonstrated in terms of treating morphea. The functional principle of this therapy is based on exposing skin lesions to ultraviolet radiation, which according to its wavelength can be divided into three basic subtypes, such as UVA (UVA1 and UVA2 are distinct), UVB (broadband UVB and narrowband UVB), and UVC [32]. As it follows from the studies conducted so far, the best results in localised scleroderma therapy can be obtained when exposing patients to broadband UVA (320–400 nm), UVA1 (340–400 nm),

PUVA, and narrowband UVB (280–315 nm). Depending on the wavelength, the ultraviolet radiation is characterised by a varied penetration into the skin. UVB radiation reaches the papillary dermis, whereas UVA can penetrate skin even to the subcutis [33]. UVC radiation is not used for treatment purposes because the radiation of such wavelength has no ability to reach the dermis [32]. It is assumed that the beneficial effect of ultraviolet radiation in treating patients suffering from sclerosing skin diseases is connected with the reduction of collagen level subtype I and III within the lesions, which is a result of diminished synthesis and increased degradation of this protein [33].

Many conducted studies proved that UVA and UVB radiation enhances the synthesis of metalloproteinase extracellular matrix (MMP) in fibroblasts [34, 35]. What is more, UVA1 decreases the level of RNA TGF-β, blocks the receptor for this cytokine, stimulates the expression of SMAD7, increases the level of IFN-γ and HO-1 (Heme Oxygenase-1), reduces the synthesis of IL-6 and IL-8 (interleukin 6 and 8), and decreases the activity of hydroxyproline. Moreover, the radiation of this wavelength diminishes the amount of Langerhans cells, T lymphocytes, and mast cells and raises the amount of CD34+ dendritic cells in the skin [35–37]. On the other hand, UVB radiation stimulates synthesis of α-MSH (α-melanocyte-stimulating hormone) receptor, which leads to an increased production of MMP-1 [38].

UVA1

Source literature comprises a series of unrelated studies proving the effectiveness of practicing UVA1 radiation in treating morphea. No optimal schedule of treatment with UVA radiation has been determined so far. There are commonly distinguished three types of treatment based on the radiation dose – low-dose (10–20 J/cm^2), medium-dose (30–50 J/cm^2), and high-dose therapy (60–130 J/cm^2) [10].

Another distinction can be made on the basis of a cumulative dose of radiation, where a small dose is below 300 J/cm^2, medium is within the range of 300 J/cm^2 to 975 J/cm^2, and high dose is from 975 J/cm^2 up to 1840 J/cm^2 [39]. The effectiveness of the abovementioned doses was reviewed in a prospective research conducted on a group of 32 patients suffering from localised scleroderma. Among the patients treated with low-dose radiation (13 patients) clinical recovery described as "fair to good response" (improvement from 26% up to 100%) amounted to 46.2%. A clearly better response was noticed in the group of patients subjected to the therapy with a medium-dose of UVA1 radiation (a similar clinical recovery for 72.7% of the group) and a medium-dose increased next to a high-dose of UVA1 radiation (considerable improvement for 70% of patients). Adverse reactions related to the therapy, such as erythema, less often pruritus, burning sensations, or tenderness, were noticed among 15% of the patients. In the case of one patient a polymorphic light eruption (PMLE) was diagnosed, which resulted in excluding that patient from further treatment. A considerably worse response to the therapy was noticed in the group of patients with higher skin phototype according to Fitzpatrick's scale (type IV–VI) [40].

The efficacy of the treatment in cases of patients with higher melanin content in the skin (skin phototype IV–VI) has not yet been explicitly determined. It is commonly considered that the beneficial effects resulting from phototherapy may be limited in such a population of patients due to the reduced skin penetration depth of the UVA radiation. However, in retrospective research conducted on a group of 101 patients (47 patients suffering from morphea among them) treated with UVA1 radiation, no statistically significant distinction was determined between characteristic skin phototypes and response to the clinical treatment and an average effective cumulative dose [41].

On the other hand, the aforementioned mechanism would explain the limited efficacy of a high-dose UVA1 radiation in treating localised scleroderma. Wang et al. proved the decrease of type I and type III procollagen mRNA levels and upregulation of mRNA of MMP-1, -3, -9 lasting for a duration of, respectively, 7 or 3–5 days after a single exposition to a high-dose of UVA1 radiation (130 J/cm^2). Simultaneously, it was noticed that recurring irradiation is related to a worse response to the therapy, while in the case of patients with naturally darker skin types no changes in procollagen and MMP levels were noticed. Having performed a clinical assessment of 12 patients treated with a high-dose of UVA1 radiation three times a week for a period of 14 weeks, a reduction in skin hardness according to the Rodnan scale has been observed in nine cases. Full recovery defined as a remission of all the lesions was not noticed among the study group. There was no response to the treatment in the case of three patients. The abovementioned results suggest a very moderate effectiveness of high-dose UVA1 phototherapy. In the same research a medium-dose UVA1 therapy was used and the results were very much alike, and it can be explained with a suntan that occurred at a later time [42].

According to the highest risk of adverse effects occurrence and limited efficacy of a high-dose UVA1 radiation, a great deal of research has been conducted assessing the usefulness of low-dose and a medium-dose UVA1 radiation in treating localised scleroderma. Prospective studies, in which a medium-dose UVA1 radiation was used in morphea therapy and comprising a study group

of 56 patients, proved a statistically significant decline in scoring according to modified Rodnan skin score (mRSS), enhanced skin elasticity measured with a Cutometer [43, 44], and a considerable reduction in dermis thickness examined with ultrasound measurements [44, 45]. Patients were exposed to radiation from three to five times a week for a duration of three to six weeks [43, 44] or 10 to 15 weeks [45]. It appears that a longer duration of the therapy is more beneficial because in the case of a shorter treatment period not all the patients responded to the therapy [43] or no full remission of the lesions was accomplished [44]. During the therapy, no serious side effects were noticed that would indicate the necessity for earlier termination of the treatment. Some reports suggest also the potential effectiveness of using low-dose UVA1 radiation. Source literature provides a series of three case studies of treating plaque-type localised scleroderma, in which low-dose UVA1 (20 J/cm^2) phototherapy resulted in full remission not only of active plaques but also of older sclerotic lesions [46].

Promising effects were also obtained providing a combination therapy of a low-dose UVA1 irradiation with calcipotriol. Kreuter et al. [47] compared the effectiveness of a low-dose (20 J/cm^2) and a medium-dose (50 J/cm^2) of UVA1 therapy and narrowband UVB radiation (NB UVB) in treating morphea. In the study, which included 64 patients divided into three unequal groups, every group was subjected to a different treatment – 27 patients were treated with a LD (low-dose) UVA1, 18 patients were treated with a MD (medium-dose) UVA1, and 19 patients were subjected to NB UVB radiation. Irradiations were performed five times a week for a duration of eight weeks. The phototherapy with narrowband UVB radiation was considerably less clinically effective than treatment with MD UVA1 radiation; simultaneously there was noticed no statistically significant difference between clinical effectiveness of LD UVA1 and NB UVB therapy. An improvement in histopathological assessment was observed in all three groups of patients [47].

Despite the remarkably high efficacy of phototherapy in treating localised scleroderma, the risk of recurrence after successful UVA1 radiation therapy is relatively high and amounts to 46% for such morphea subtypes as generalised, linear, plaque-type, and mixed. It has been determined that the risk of recurrence increases along with the duration of the disease and should not be associated with morphea subtype, skin phototype, age of onset of the disease, magnitude of the cumulative dose, and duration of the treatment [48].

PUVA (psoralen UVA)

Psoralen UVA is a treatment method consisting of concurrent usage of UVA1 phototherapy and application of a chemical substance that increases the sensitivity of the skin to UVA radiation. It has been proven that psoralen sensitises DNA of the cells to the UV radiation, is involved in the production of reactive oxygen species, suppresses proliferation and induces apoptosis of T-lymphocytes and keratinocyte cells, and triggers antigen-presenting cells apoptosis. Additionally, it reduces the expression of HECA (homing receptor) on lymphocytes, decreases the synthesis of IL-2, modulates the expression of other cytokines and their receptors, and stimulates melanogenesis [49].

The most commonly used substance is 8-methoxypsoralen (8-MOP), which can be applied per os or used locally as an aqueous solution, ointment, cream, or gel. Topical treatment with psoralen gives a possibility to avoid systemic adverse reactions, such as gastrointestinal complications manifesting as nauseas and vomiting. Limited duration of contact and precisely determined area of sensitised skin being in contact with the substance contributes to the reduced risk of sunburn occurrence. In source literature can be found case studies proving the effectiveness of PUVA therapy in treating severe, rapidly progressing, and resistant to standard therapies forms of localised scleroderma both in children [50, 51] and in adult patients [32, 51]. Some researches indicate also a possible efficacy of PUVA therapy in treating Parry-Romberg syndrome, which has many common features with localised scleroderma type en coup de sabre [52]. Source literature provides three prospective studies assessing the effectiveness of phototherapy in combination with psoralen on the group of 24 patients suffering from various types of morphea.

Buense et al. [53] conducted research evaluating the effectiveness of topical PUVA, systemic PUVA, and NB UVB therapy in treating varied types of localised scleroderma. The study group consisted of 13 patients suffering from morphea in varied stages. The effectiveness of each phototherapy was estimated on the basis of the organoleptic assessment performed in accordance to the Rook clinical scoring system and ultrasound measurements (7–14 MHz). No significant difference in treatment effectiveness was noticed depending on the type of provided phototherapy. During clinical assessment, there was observed a reduction in skin hardness in all the lesions. Ultrasound examination proved the decrease of dermal thickness in all early inflammatory lesions except one. In case of stable late lesions such a decrease was observed only in seven focal lesions. It is also worth mentioning that for particular patients the primary thickness of the skin was less than normal in the area of late lesions. Further reduction in dermis thickness resulted probably from an intensified collagen degradation caused by phototherapy [53].

In the second, considerably smaller prospective study consisting of only four patients, a cream was used containing 8-methoxypsoralen (8-MOP) of varied concentration depending on the skin phototype – concentration 0.001% for patients with skin phototype I or II and 0.0025% for patients with skin phototype III or IV. Patients were subjected to the therapy four times a week for a duration of eight weeks. The treatment included application of the cream on the lesion an hour before exposing it to the UVA1 radiation. At the beginning of the therapy patients were exposed to a low-dose radiation, representing 30% of the determined earlier minimal phototoxic dose (MPD), and the dose was gradually increased to the value of 3.5 J/cm^2 (a cumulative dose of radiation was within the range of 67.5–121 J/cm^2). The undertaken treatment resulted in full recovery or significant reduction of skin hardness proven in palpation or ultrasound examination. Improvement was also noticed in histopathological evaluation (dermal collagen structure was determined to be approximately normal) [54]. Both the abovementioned studies proved no early adverse reactions, which indicates a favourable safety profile of the therapy resulting from low doses of the applied radiation [53, 54].

However, we cannot eliminate the risk of side effects remote in time such as a higher risk of occurrence of squamous and basal cell carcinoma of the skin [55, 56]. According to source literature it also seems beneficial to provide a PUVA therapy in combination with calcipotriol ointment, even in cases of severe localised scleroderma [25].

Photodynamic therapy

Another treatment method based on a combination of a photosensitising agent and UV radiation is a photodynamic therapy. The main assumption of this method is to produce reactive oxygen species as a consequence of activating a photosensitive substance under aerobic conditions. As a result of this phenomenon death of the cells follows in the way of apoptosis or necrosis and modification of transcription and translation under photo-oxidative stress. In dermatology three major photosensibilators are used: sodium porfimer, 5-aminolaevulinic acid (ALA), and methyl aminolevulinate (MAL). It has been also proven that the photodynamic therapy stimulates directly and indirectly the synthesis of metalloproteinase extracellular matrix, which can explain its effectiveness in treating morphea [57, 58].

Source literature provides two prospective studies assessing the effectiveness of treating localised scleroderma with photodynamic therapy. Karrer et al. [59]. conducted research in which were included five patients suffering from morphea resistant to previously undertaken treatment. The therapy consisted of application of a 3% gel with ALA on the lesion under occlusion and after six hours of exposing the lesion to a low-dose radiation from an incoherent light source (10 J/cm^2). Patients were subjected to the treatment once or twice a week for a duration of three to six months. In every instance, a significant clinical improvement was noticed and proved in compliance with the Rook scoring system, and a reduction in skin hardness was measured with a durometer. Simultaneously, in the case of all the lesions that were not subjected to the therapy, no significant changes were noted. During the two-year observation period neither recurrence nor progression of the disease was noticed in any of the patients [59].

In another prospective research the effectiveness of the photodynamic therapy was evaluated on a group of six patients. At the beginning a 20% ALA gel was applied on the lesion under occlusion, and after five hours the lesion was exposed to a low-dose radiation from a broadband incoherent light source (25 J/cm^2). Every patient was exposed to seven irradiations, which were performed once a week. The effectiveness of the photodynamic therapy was evaluated with palpation, and histopathological examination and skin hardness was also measured with a durometer. In the group of patients who underwent full therapy, in the case of four patients there was observed a significant improvement. However, it must be mentioned that similar changes were noticed in the areas of lesions that were not subjected to the therapy, so the possibility of spontaneous remission of the disease cannot be eliminated. Having measured the thickness of the skin with a durometer it was observed that skin hardness reduced only in two cases, while in the rest of the patients it increased during the therapy. It must be underlined that a relatively low efficacy of the treatment might have been a result of many limitations of the conducted research, such as a scarce study group or a short duration of performed irradiations. During the therapy, many side effects were observed i.a. erythema, burning sensations, and pruritus [60]. Obtained results are in contradiction with observations noticed and described in the research conducted by Karrer et al., during which the only noted adverse reaction was hyperpigmentation within the radiated lesions. It seems that photodynamic therapy may be beneficial in treating morphea, but it has not yet been clearly proven.

Conclusions

All the aforementioned treatment methods used in localised scleroderma therapy are characterised by varied effectiveness and can be summarised in a subjective manner in the Table I.

However, there has been developed no causal treatment for morphea of well-proven effectiveness so far, and schedules of symptomatic treatment are not yet clearly determined and are still a subject of discussion. This is mainly a consequence of a shortage of methods for precise and objective assessment of lesion intensity, relatively low number of patients suffering from morphea, and a tendency for the disease to remit spontaneously, which undoubtedly obstructs conducting any research on the subject of this disease entity treatment. The major advantage of the topical therapy is a relatively favourable safety profile and a potentially high effectiveness of the treatment, but there is still a genuine need to conduct further randomised placebo-controlled trials.

Table I. Efficiency of various treatment methods used in localised scleroderma therapy

Treatment method	Method efficiency
Topical and intralesional corticosteroids therapy (only for active inflammatory lesions)	+
Combination therapy with calcipotriol	
Topical corticosteroids with calcipotriol	+ +
Phototherapy with calcipotriol	+ +
Topical calcipotriol monotherapy	+
Calcineurin inhibitors (topical tacrolimus therapy)	+ +
Topical imiquimod	+
Intralesional IFN-γ	–
Phototherapy	
UVA1 phototherapy	+ + +
PUVA (psoralen UVA) therapy	+ + +
Photodynamic therapy	+

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