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Role of UVA1 phototherapy in treatment of scleroderma and scleroderma-like disorders

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Abstract

Treatment of scleroderma and scleroderma-like diseases poses a serious challenge to contemporary dermatology due to the complexity of its pathogenesis, low incidence of the diseases and their heterogenous clinical expression. the manifestation of this autoimmune disease includes an increased production and deposition of collagen fibres types I and III in the skin and connective tissue as well as vascular alterations. Ultraviolet A1 (UVA1) phototherapy affects various stages of a morbid process in scleroderma: it inhibits inflammation and affects the consequences of it, fibrosis. Currently, UVA1 is proposed as a potential treatment and is believed to have a multifold mechanism of action. This includes, inducing apoptosis in T and B lymphocytes, inhibition of proinflammatory cytokine production and ability to induce collagenase production by fibroblasts. UVA1 irradiation may also interact with endothelial cells, promoting angiogenesis. Efficacy of high, moderate, and low doses of UVA1 was documented. Advantages of UVA1 phototherapy include the evident avoidance of systemic side effects of psoralens such as nausea and vomiting or photokeratitis as well as lower risk of phototoxic reactions with deeper penetration of radiation. Its disadvantages include high cost of equipment, thus reducing the accessibility of the treatment to specialized centres. Due to its unique mechanism of action, attempts to use UVA1 phototherapy seem justified in other rare diseases, developing with skin induration.

Key words: *phototherapy, UVA1, treatment, scleroderma, morphea, lichen sclerosus, scleredema, scleromyxedema, graft-versus-host disease.*

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Introduction

Treatment of scleroderma and scleroderma-like diseases poses a serious challenge to contemporary dermatology due to the complexity and of its pathogenesis, low incidence of the disease and its heterogenous clinical expression. Recent treatment regimes, which include immunosuppressant drugs, produce many undesirable effects. Introduction of photochemotherapy (psoralen + ultraviolet A – PUVA) followed by ultraviolet A1 (UVA1) phototherapy (which affects the fibrotic process) significantly enriched the therapeutic panel. In Poland, however, application of phototherapy in the indications remains still insufficiently widespread [1, 2].

Lamps which emit narrow range, long wave UVA-1 radiation of 340-400 nm were produced in 1981 by Mutzhas *et al.* In 1992 Krutmann *et al*. published positive results of treatment of atopic dermatitis (AD) using high doses of UVA1 [3, 4]. At present, AD represents a standard indication for such therapy, formulated in modern consensus recommendations [5-7]. The other group of diseases in which UVA1 may be of therapeutic importance are fibrotic diseases such as generalised morphea.

Treatment of various connective tissue diseases took advantage mainly of wide range UVA (broad band UVA – BB UVA), PUVA photochemotherapy, and UVA1. Ultraviolet A1 offers deeper penetration compared to that obtained with UVB as well as targeting fibrosis and other structures, i.e. fibroblasts, T-lymphocytes, Langerhans cells, mast cells, endothelial cells. Broad band UVA and PUVA radiation (range of 315 to 400 nm, max. 340-360 nm) reach-

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es papillary layer of dermis while UVA1 (range of 350 to 400 nm, max. 365-375 nm) acts deeper in the dermis and even in the subcutaneous tissue. Moreover, around 20% of the radiation reaches vascular system which, according to some authors, provides grounds for a potential systemic action of this radiation range [8].

Pathogenesis of scleroderma

Manifestation of this autoimmune disease includes an increased production and deposition of collagen fibres types I and III in the skin and connective tissue as well as vascular alterations and an autoimmune process. The more localised form of the disease (morphea) differs from systemic one in such a way that it does not involve inner organs. However, the skin lesions in both are histologically identical. As a chronic disease, morphea does not affect longevity of patients but it definitely affects quality of patient's life. Depending on its form, orthopedic, neurologic and ophthalmologic complications may arise [9-11].

The pathogenesis of morphea remains unclear. Its clinical presentation involves an excessive fibrosis due to a disturbed turnover of the extracellular matrix. However, vascular lesions and immune system activation, including autoaggressive processes are developed prior to clinical evidence [12-16]. Although the initiation of the process remains unknown, possible risk factors include a specific, genetic background and various types of environmental factors (e.g. infectious factors, *Borrelia burgdorferi*, physical factors, e.g., trauma, radiotherapy, chemical factors, e.g., bleomycin, silica [15, 17-22]. Currently, it is suggested that the first stage of the disease involves injury of endothelial cells. This ultimately leads to their apoptosis and a lowered vascular density, which are associated with an infiltrate of inflammatory cells [12, 13, 23, 24]. The phenomena are accompanied by elevated serum concentration of adhesion molecules, including selectins E and P, vascular cell adhesion molecule (VCAM)-1, and intercellular adhesion molecule (ICAM)-1 [25-27]. The stimulated endothelial cells, cells of inflammatory infiltrate, and finally activated fibroblasts provide the source of several cytokines and growth factors which may participate in pathogenesis of the disease. This include profibrotic factors [transforming growth factor β – TGF-β, connective tissue growth factor (CTGF), interleukin 4 (IL-4), IL-13], angiogenic factors [IL-8, vascular endothelial growth factor (VEGF)], and proinflammatory factors [IL-1, tumor necrosis factor α (TNF-α)] [27-29]. In parallel, a lowered production is postulated of cytokines manifesting antifibrotic properties, such as interferon γ (INF-γ) [30, 31]. However, attempts to introduce the latter to morphea treatment did not show favourable results. Additionally, soma cases of induced type SSc in multiple sclerosis patients treated with INF-γ were found [28, 31]. Moreover, intensified deposition of extracellular matrix components, including collagen I and III, fibronectin, glycosaminoglycans depends on their intensified production and, on diminished decomposition by matrix metalloproteinases [14, 32-35].

Recognition of individual stages of the complex pathogenesis is indispensable for any search aimed at detecting potential targets for new therapeutic approaches. Despite numerous investigations, the therapeutic potential still remains restricted. The currently accepted therapy focuses on controlling individual pathogenetic phases, i.e. the inflammatory, vascular, or fibrotic phase, using glucosteroids, penicillamine, derivatives of vitamin D, tacrolymus, methotrexate and other drugs. In more severe cases, however, linked approaches provide better results, e.g., association of glucocorticoid anti-inflammatory action with methotrexate-induced immunomodulation [9-11].

Phototherapy in morphea

In 1994, Kerscher *et al*. applied photochemotherapy for the first time using PUVA bath in two patients with morphea, employing 20 exposures 4 times per week for 6-8 weeks followed by 10 exposures twice a week, which resulted in both clinical and histological improvement [36]. One year later the same author treated 10 patients applying UVA1 phototherapy with a low dose of 20 J/cm2 4 times a week for 6 weeks, and noting improvement after 15 exposures and a significant improvement following 24 exposures in over 80% foci of morphea [37]. In 1998 Kerscher *et al.* again reported a good effect of treatment in 30 patients administered with a low dose of UVA1 (20 J/cm^2 for 12 weeks with 30 exposures to the total dose of 600 J/cm^2) [38]. Egyptian investigators, El Mofty *et al*. in 2000 examined application of low, wide spectrum UVA doses (applicable in a PUVA chamber) in 12 patients with 20 exposures and obtained a good effect [39]. In 2004, the same authors compared various doses of wide spectrum UVA (5-10-20 J/cm^2) in consecutive 16-21-26 patients who received 20 exposures and detected better response in treatment of fresh foci [41] Stege *et al.* in 1997 conducted comparative studies on 10 patients with morphea, treated with a high UVA1 dose of 130 J/cm^2 and receiving 30 exposures to the total dose of 3900 J/cm^2 vs. 7 patients treated with a low dose of 20 J/cm^2 and receiving 30 exposures (total dose of 600 J/cm^2), demonstrating better results at higher dosages, compared to the lower dose [42]. At the end of 2006 the most valuable comparative study was published. A randomized study including 64 patients in three groups, treated consecutively with a low UVA1 dose, a moderate dose of UVA1 and a narrow band of UVB. The study demonstrated superiority of UVA1 over UVAB doses in clinical, histologic and high frequency ultrasonographic (HF USG) appraisal [42]. Subsequently, a few reports were published which confirmed usefulness of moderate UVA1 doses [43, 44]. In 2009, Anders *et al.* compared also a very significant retrospective study on 17 patients treated with mod-

erate doses of UVA1 in the period between 6 month and 3 years earlier which demonstrated positive short- and long-term effects in clinical, HF USG, elastometric appraisals as well as comparing levels of collagen and its metabolites in serum and urine before and after the treatment [45].

In 2011, the paper of Pereira *et al.* appeared, dealing with evaluation of efficacy in treatment using low doses of UVA1 (the mean of 31 J/cm^2, on the average 33 exposures, the mean total dose of 1662 J/cm^2) in patients with various forms of scleroderma. The study included 21 patients: 11 patients with plaque-type morphea, 3 patients with linear morphea, 2 patients with generalized morphea, one patient with deep morphea, one 10-year old patient with pansclerotic morphea of children, and 3 patients with systemic sclerosis. The best clinical effect was obtained in the group of patients with plaque-type morphea, followed by patients with linear and systemic disease. A moderate effect was obtained in generalized morphea, poor effect in pansclerotic morphea while no response to treatment was seen in its deep form [46].

Pansclerotic morphea of children represents the only exception, in which according to recommendations UVA1 phototherapy can be applied in children below 18 years of life. In 1997, Gruss *et al.* reported positive effect of treatment with low UVA1 doses of 20 J/cm^2, 4 times a week for 8 weeks, including 32 exposures to the total dose of 640 J/cm^2 [47]. In the opinion of some authors, specific forms of scleroderma (i.e. deep scleroderma, en coup de sabre, and eosinophilic fasciitis) require systemic therapy due to the depth of developing process [48]. Literature on the subject contains description of a 44-year-old female with eosinophilic fascitis accompanied by a toxic liver injury due to cyclophosphamide treatment, treated with a moderate dose of UVA1 (60 J/cm^2, 31 exposures, 3× a week, linked to low 5 mg doses of prednisone). A good tolerance of the treatment and improvement in HF USG and elastometry was demonstrated [49].

Systemic sclerosis

In 2000, Morita *et al.* irradiated skin lesions within forearms of 5 patients with systemic sclerosis (SSc), using a moderate UVA1 dose of 60 J/cm^2, 30 exposures. They achieved an improvement on skin temperature, elasticity, histological skin patterns, as well as an increased passive mobility in joints [50].

In 2000, subsequent authors, von Kobyletzki *et al.* treated the hands of 8 patients with low doses of UVA1 of 30 J/cm^2 4 times a week for a total of 50 exposures. Seven out of 8 patients showed a significantly improved mobility and healing of ulcerations [51]. In 2004, Kreuter *et al.* irradiated a group of 18 patients with acrosclerosis using low dose of UVA1. They achieved improvement in 16 out of 18 patients as well as increased activity of collagenase and absence of relapses in a six month observation [52]. Recently, in a letter to editors a case description was published related to an excellent effect of a whole body irradiation using a moderate dose of UVA1 up to the total dose of 2225 J/cm^2 in a female patient with systemic sclerosis on microstomia type lesions [53].

Mechanism of UVA action in skin lesions of scleroderma

Ultraviolet A1 phototherapy is a method affecting various stages of the sclerodermal process. The therapy inhibits the inflammatory process, thus preventing the progression of the disease as well as altering fibrosis, an effect of the disease. The currently accepted mechanism incorporates several aspects, including:

1) immunomodulating activity by inducing apoptosis,
2) effect on production of proinflammatory cytokines,
3) ability to induce production of collagenase by fibroblasts,
4) interacting with endothelial cells, promoting angiogenesis.

Apoptosis occurs in T and B lymphocytes, as well as in immature proliferating mast cells. Krutmann and Morita suggested that induction of apoptosis in T lymphocytes under the effect of UVA1 represents the mechanism of action manifested by the treatment in AZS. A particular propensity for apoptosis is manifested by lymphoma T cells, which has found application in treatment of cutaneous T-cell lymphoma (CTCL), in which UVA1 may be equally or even more effective than PUVA [54]. In early stages of morphea apoptosis involves mainly T and B lymphocyte infiltrate. In later stages it may affect also fibroblasts, which has been demonstrated in *in vitro* tests [55]. Moreover, two mechanisms of the early and late apoptosis, respectively, have been distinguished. In early apoptosis, UVA induces active oxygen molecules (ROS), exerting indirect action on cell DNA which is not seen after PUVA treatment. According to Morita *et al.*, the singlet oxygen induces expression of Fas/Fas ligand molecules at the surface of lymphocytes T. Studies on Jurkat cells demonstrated that singlet oxygen affects mitochondria, opening cyclosporine A (CyA) CyA-sensitive megachannels, which results in a decreased membrane potential of the cell and release of AIF, the apoptosis-initiating factor. Superoxide anions injure the mitochondrial megachannels while release of cytochrome C leads to CyA-independent apoptosis [48].

In contrast to UVB, UVA1 does not increase levels of serum IL-10 but it decreases concentration of proinflammatory cytokines, i.e. IL-12, responsible for antibody-dependent cytotoxicity, activation of T lymphocytes and eosinophils. It induces IL-1 which, in turn, influences production of IL-6, increasing the level of collagenase production by fibroblasts.

The ability to increase production of collagenase by fibroblasts was originally demonstrated in *in vitro* studies. In fibroblast cultures exposed to UVA1, an increase in collagenase production took place (expression of collagenase I mRNA) in a dose-dependent manner [56]. Subsequent

studies in *in vivo* skin biopsies containing morphea lesions after a cycle of irradiation with a high dose of UVA1 demonstrated a twenty-fold increase in expression of collagenase I mRNA [57].

UVA decreases activity of prolyl hydroxylase, responsible for stabilization of the collagen triple helix, it may also inhibit formation of cross-links within collagen fibres (55).

Ultraviolet A decreases expression of collagen I, collagen III and TGF-β genes (*COLI*, *COLIII*, *TGFB*) and increases expression of matrix metaloproteinases (MMP) and IFN-γ. Decreased production of collagen involves not only collagen type I but, as shown in earlier studies, also collagen type III [58].

Effect of endothelial cells was studied in skin biopsies taken from 4 patients with morphea before and after a cycle of exposures to UVA1 using a low dose of 30 J/cm^2, 4 times a week for 8 weeks and, then, 3 times a week for 6 weeks up to the total dose of 1500 J/cm^2. In immunohistochemical experiments on angiostatic, angiogenic, and angioapoptotic factors; UVA1 was demonstrated to induce angiogenesis and to decrease apoptosis in endothelial cells [59].

Scleroderma-like diseases

Due to the above mechanism of action UVA1 phototherapy may be utilised in other rare diseases progressing with induration, linked to an immunological background, such as lichen sclerosus, chronic sclerodermoid graft versus host disease (cGvHD) and other like scleromyxoedema, scleroedema Buschke, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) or nephrogenic fibrosing dermopathy (NFD).

Lichen sclerosus is uncommon, sclerosing inflammatory dermatosis of unclear etiology which affects skin and genital mucous membranes. In some cases whitish papular lesions may overlap sclerotic plaques typically seen in morphea. Originally, efficacy of phototherapy was noted in cases of overlapping morphea and lichen sclerosus lesions. Subsequently, PUVA baths and low doses of UVA1 were applied in cases of non-sexual form of lichen sclerosus, resistant to externally applied steroids and/or calcineurin inhibitors. In two patients with lichen sclerosus treated with low doses of UVA1, Kreuter *et al.* observed regression of skin lesions within 10 months and an evident improvement in HF USG patterns [62]. The same authors subsequently described 10 patients treated with low doses of UVA1, 20 J/cm^2, 4 times a week for 10 weeks. Evident clinical improvement took place, confirmed by HF USG patterns, and one-year observation demonstrated relapse of lesions in only two patients [63]. Literature of the subject contains also descriptions of PUVA applied topically with a cream and applications of UVA1 in lichen sclerosus in the genital regions. In such cases, however, great caution is recommended due to an increased risk of squamocellular cancer development [64].

Graft-versus-host disease (GvHD) represents an autoimmune disease and its advancement ranges from local lesions to erythroderma with development of blisters, like in the toxic epidermal necrolysis. It is caused by immunocompetent lymphocytes from the grafted tissue that are capable of proliferation and attacking the host organs, such as the skin, liver and intestines. The chronic GvHD (cGvHD) which developes after 100 days most frequently occurs as a transition from acute GvHD but it may develop independently of the acute form. Skin and mucous membranes are involved in over 90% of cases and the skin may be one of the first organs involved. The skin lesions observed in cGvHD may resemble those seen in the course of lichen planus (the lichenoid form) or those in the course of scleroderma (the sclerodermoid form of GvHD). The latter form may lead to restricted mobility of joints and development of ulcerations. In prophylaxis and treatment of GvHD immunosuppressive drugs are employed, such as cyclosporin, glucocorticoids, tacrolymus, mofetil mycophenolate [65]. Unfortunately, their side effects include risk of infections and secondary tumours. Therefore, alternative methods of treatment are recommended, such as those employing immunomodulatory effects of ultraviolet radiation. To a certain extent, they may allow reduction in applied doses of immunosuppressants or even their substitution. Various methods of phototherapy were employed in treatment of acute and chronic GvHD, including extracorporal photopheresis (ECP), PUVA with oral administration of psoralen, PUVA baths, UVA1 and UVB. Similarity of the lesions to lichen planus provided rationale for application of PUVA photochemotherapy in treatment of the lichenoid form. Literature on the subject contains reports on efficacy of the method applied in parallel with an immunosuppressant treatment. However, efficacy of PUVA in treatment of the sclerodermoid form is not so evident. PUVA is suggested to be more effective in decreasing skin thickness while improvement in joint mobility used to be obtained employing UVA1 [66]. Literature on the subject contains few reports on application of UVA1 in treatment of cGvHD. Some of them demonstrated a significant improvement in reduction of dermatogenic contractures, partial remission of the lesions but some of the authors failed to obtain the therapeutic effect [67-74]. Unfortunately, an objective appraisal of efficacy in phototherapy remains practically impossible due to a frequent need to link it to immunosuppression and absence of generally accepted forms of grading the skin lesions. As compared to photochemotherapy, advantages of UVA1 therapy include: no need to apply psoralen and lower risk of phototoxic reactions, particularly in patients with hepatic involvement in the course of GvHD. However, due to the possible distant complications in the diseases, i.e. CTCL or GvHD, the ratio of advantages to risk should always be considered and, therefore, parallel treatment with CyA should be avoided [75]. In our centre a 44-year-old male lymphoma patient developed chronic sclerodermoid

and, then, lichenoid form of GvHD after receiving a bone marrow graft from his sister. Originally, scleroderma-like lesions dominated and resulted in a restricted mobility in joints and the patient was treated with CyA. PUVA applied in 2009 brought a negligible effect. In 2009 the patient was exposed to the first cycle of UVA1 exposures, at 40 J/cm^2, 30 exposures up to the total dose of 1070 J/cm^2. This treatment brought a significant improvement of contractures and permitted a decrease of dose and eventual elimination of CyA. During this time, patient remained under the care of haematologists. In 2010, a subsequent course of UVA1 exposures, at 30 J/cm^2, 18 exposures up to the total dose of 430 J/cm^2 yielded less advantageous effect on lichenoid lesions, which, on the other hand, reacted very well to low systemic doses of glucocorticoids.

Scleromyxedema is a rare, chronic and progressive disease which may involve the skin and other internal organs. Is characterised by a generalised papular and sclerodermoid eruption, the presence of mucin deposition of reticular dermis, fibroblast proliferation and fibrosis with an absence of a thyroid disorder, often accompanied by monoclonal gammapathy. Response to treatment with cyclophosphamide and steroids used to be unsatisfactory [76]. Literature of the subject contains few papers on application of UVB and PUVA in treatment of the disease. In 1984, Farr described 20 patients treated with BB-UVB and PUVA baths and demonstrated better results using PUVA while UVB even exacerbated course of the disease in one case [77]. Subsequently, PUVA photochemotherapy was applied as well as parallel application of PUVA and melphalan or PUVA and systemic steroids, noting general improvement but also a case complicated by appearance of multiple keratoacanthomas and development of SCC [78]. Until now, no cases of scleromyxedema treated with UVA1 were published except of a single case of a mild disease, in which a moderate clinical improvement was observed [79].

Scleredema is another rare condition characterised by induration of the skin and erythema which sometimes may be associated with the history of febrile illness-called scleredema Bushke or diabetes. The literature contains reports on efficacy of PUVA baths, local PUVA and ECP. In 2004, Janiga *et al.* applied low doses of UVA1 in 2 patients with scleroedema in diabetics and scleroedema Bushke and observed disappearance of lesions [80]. Tuchinda *et al.* in 2006 irradiated 6 patients (including 5 patients with diabetes mellitus) with low and moderate dose of UVA1. Five patients completed the treatment with a moderate or good results, where one patient suffered from a relapse after 15 months [81]. Eberlein-Konig *et al.* in 2005 described a single case treated with a moderate UVA1 dose (50 J/cm^2) with clinical improvement, confirmed by HF USG patterns [82].

The syndrome of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) is a very rare disease associated with the presence of indurating skin lesions. One severe case was described which was found to be resistant to standard chemotherapy, but showed improvement following 35 exposures to low UVA1 doses [83].

Nephrogenic fibrosing dermopathy (NFD) is a disease of fibrosis of the skin and internal organs that occurre in patients with renal insufficiency. A 47-year-old female patient was described, suffering from for 2 months who was treated with high dose UVA1 dose 12 weeks. A good clinical effect was obtained, confirmed by biopsy of the altered skin before and after exposures as well as of normal skin. Amounts of collagen were estimated by determination of hydroxyproline level as well as expressions of mRNA for procollagen I, collagen III, TGF-β and CTGF were compared [84].

Discussion

It seems that both systemic photochemotherapy, PUVA baths and UVA1 show favourable effects in treatment of some types of morphea. In further studies it will be significant to compare the two methods in their efficacy and safety. Although UVA1 therapy has not been evaluated in systemic sclerosis under setting of randomized clinical trials, small open studies and single case reports indicate that UVA1 therapy might be of benefit in treating skin involvement in patients with systemic sclerosis. Up to date no efficacy of UVA1 with respect to SSc-related internal organ involvement has been reported.

The high, moderate and low doses of UVA1 were found to be effective. Some authors regard moderate doses as the optimum solution while other stress significance of low doses, which is a more accessible treatment. However, it still remains unknown whether the positive effect reflects the applied daily dose, in a standard way subdivided to low doses of UVA1, < 20 J/cm^2, moderate doses of UVA1, 20-90 J/cm^2, high doses of UVA1, 90-130 J/cm^2 or the total dose, also subdivided to low (TD < 300 J/cm^2), moderate (TD 300-975 J/cm^2) and high (TD > 975 J/cm^2) doses.

Obviously, it should not be expected that scleroderma lesions will fully regress leaving a healthy looking skin. At the preliminary phase the therapy aims rather at restricting the inflammatory process, manifested by presence of the liliac ring and at softening of the sclerotic plaques. The frequently noted phenomenon involves manifestation of post-inflammatory hyperpigmentation. The sclerotic plaques manifest a tendency for pigmentation more accentuated than that of the normal skin and clinically undetectable foci of the disease may become apparent following a cycle of exposures and the patient should be informed about it [60]. Some authors suggest also that patients with shorter anamnesis and a lighter phototype respond better to the treatment [61].

According to American authors, the first line of treatment for generalized morphea should involve phototherapy, dependent on accessibility (UVA1, BB UVA or possibly NB UVB, dependent on accessibility and other factors).

This treatment provides a better safety profile, when compared to methotrexate or systemic glucocorticoids [10, 11]. The method of UVA1 is free of side effects, associated with psoralen application, that is required in standard PUVA therapy and has reduced phototoxic effects. Disadvantages include high cost of the equipment and accessibility restricted to specialized centres.

Ultraviolet A1 phototherapy seems to offer a promising approach to treatment of some types of morphea, skin involvement in systemic sclerosis as well as other rare fibrotic dermal diseases. Unfortunately, rational basis for such a treatment is based on descriptions of individual cases or their short series. Therefore, further, multicentre studies are required to more accurately define treatment schedules. Presently, due to the high cost of equipment required for UVA1 phototherapy, such treatment represents a valuable supplementation of standard phototherapy approaches in centres which have at their disposal the respective equipment.

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