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Original Paper

RETROSPECTIVE COHORT STUDY COMPARING EFFICACY AND SAFETY OF PHARMACOLOGICAL INTERVENTION AND PHOTOTHERAPY IN MODERATE TO SEVERE PSORIASIS PATIENTS IN A REAL-WORLD SETTING

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Methotrexate (MTX) is one of the first-line systemic treatment options in patients with moderate-to-severe plaque psoriasis and can be combined with narrow band UVB phototherapy (Nb-UVB). However, such a combination is rarely used for optimal duration due to safety and efficacy concerns. The aim of this study was to assess efficacy and safety of methotrexate (MTX) combination with low doses of Nb-UVB versus MTX monotherapy in patients with moderate-to-severe plaque psoriasis in a real-world setting. Retrospective psoriasis patient medical chart review was performed for the period from 2013 till 2019. The combination therapy group (Group 1, n = 74) received MTX 10 mg s/c once a week for four to six weeks and 311 nm UVB phototherapy according to the skin type and protocol of administration — three times a week; undergoing 10–24 procedures in the treatment course. The monotherapy group (Group 2, n = 57) was treated, using MTX as monotherapy 2.5 mg two times a day orally for five days (4–6 treatment courses in total). The combination therapy group achieved decrease of mean PASI at the end of the 2nd week of treatment by 38% vs monotherapy group 21%. Combination of low dose subcutaneous MTX and Nb-UVB therapy provides better treatment outcomes and normalisation of immunochemical parameters than for MTX monotherapy. This combination also showed a favourable tolerability profile.

Keywords: *Th 17 pathway, combined treatment, Nb-UVB, T cells, immunology.*

INTRODUCTION

Psoriasis is a chronic relapsing, genetically and immunologically associated disease with extensive epidermal proliferation, presenting with incomplete differentiation of epidermocytes, alterations in blood vessels and infiltrates of inflammatory immunocompetent cells in epidermis and the dermal papillary layer (Griffiths and Barker, 2007; European S3 guidelines, 2009; Rendon and Schakel, 2019). According to literature data, prevalence of psoriasis in the world varies from 2 to 4.9% (European S3 guidelines, 2009; Rendon and Schakel, 2019). Similar data are reported for Latvia, with growing annual incidence of psoriasis (Hartmane *et al*., 2021).

Methotrexate became widely used at least 60 years ago for treatment of severe psoriasis, including pustular psoriasis, psoriatic erythroderma, psoriatic arthritis, and for extensive chronic plaque psoriasis not controlled by conventional therapy (Boffa and Chalmers, 1996). According to literature data, methotrexate (MTX) is one of the most effective medicines in cases of vastly spread skin and joint forms of pso-

riasis (Griffiths and Barker, 2007; Rendon and Schakel, 2019). In psoriasis cases, MTX can be administered per os, intramuscular (i/m) or subcutaneously (s/c) — mean dosage of 15 mg per week is recommended (Schmitt *et al.,* 2008; Hartmane *et al.,* 2016). Among systemic drugs used in psoriasis therapy, only biological preparations are more effective than MTX. However, there are cases when MTX is used both as initial therapy before biological medicines, or in combination with them (Menter *et al.*, 2014). MTX has complex pharmacological mechanism of action, with recent studies indicating involvement of two ectoenzymes CD39 and CD73 on T regulatory cells (Tregs) cooperating together, which leads to a change in the adenosine triphosphate/adenosine monophosphate (AMP) ratio and activates the AMP-activated protein kinase signal pathway, and then affects the downstream signal pathways including the mechanistic target of rapamycin (mTOR) signalling (Carling, 2007). Also, it was discovered that MTX could significantly restore the immunosuppressive function of Tregs and prevent aberrant proliferation of T effector cells (Teffs) in patients with psoriasis, reverse downregulation of CD73, activate AMPK and inhibit the mTOR pathway, and downregulate the interleukin-17 and interferon-c levels (Yan *et al.,* 2018). This detailed research improves our knowledge of the pathogenesis of psoriasis and provides mechanistic insights into MTX pharmacology. Results of MTX safety and efficacy have been published elsewhere (Puig, 2014; Roubille *et al.*, 2015).

In psoriasis cases, phototherapy has immunosuppressive effect on functions of antigen-presenting cells and production of cytokines. It induces apoptosis also in pathogenically significant cells. Dosage of phototherapy is determined based on patient skin phenotype (Goktas *et al.,* 2006).

When initiating therapy with narrow-band ultraviolet B light (Nb-UVB), strong inhibition of the Th17 pathway by UVB was confirmed in an *ex vivo* organ culture system by demonstrating reduced signal transducer and activator of transcription 3 (STAT3) phosphorylation and β-defensin-2 production. These results were further substantiated by demonstrating that Nb-UVB inhibited Th17-dependent psoriasis-like dermatitis in mice. Other pathways affected by Nb-UVB therapy include the IFN signalling pathway, epidermal differentiation, and other well-known therapeutic targets in psoriasis, such as the glucocorticoid, vitamin D, peroxisome proliferator-activated receptor, and IL-4 signalling pathways. In conclusion, clinical improvement of psoriasis by Nb-UVB is linked to suppression of Th17 and type I and type II IFN signalling pathways, which are critical in the pathogenesis of the disease. The results show that a clinically effective Nb-UVB therapy is based on suppression of a broad range of important molecular pathways in psoriatic skin (Goktas *et al.,* 2006; Hartmane *et al.,* 2016). The inception dosage is 0.1–0.3 J/cm² 2–5 times per week, in a treatment course of 25 procedures (Rácz *et al.*, 2011).

Combination therapy of MTX with Nb-UVB has been shown to achieve skin clearance in psoriasis patients in a shorter duration of time with a favourable safety profile (Lebwohl *et al.,* 2004; Mahajan, *et al.,* 2010; Soliman, *et al.,* 2015). MTX and UVB phototherapy could provide additional benefit for patients who are not yet candidates for biological therapy in the limited reimbursement environment (Hartmane *et al.*, 2021). Despite considerable efficacy benefits, combination therapy has not been established as routine practice for treatment of moderate-to-severe psoriasis in Latvia. Up to now, data in the eastern Baltic countries on the efficacy of combined narrow-band UVB phototherapy and MTX in psoriasis treatment have not been collected.

The aim of the current study was to assess efficacy and safety of combination therapy MTX with Nb-UVB vs MTX monotherapy in a real-world clinical setting in patients with moderate to severe psoriasis.

MATERIALS AND METHODS

Single centre retrospective analysis of patient medical documentation for the period from 2013 till 2019 was performed, further selecting patients who had complete blood immunological test data for the markers of interest before initiation of therapy and at the end of therapy. Here we report extended analysis of an initial study with a larger patient cohort (Hartmane *et al*., 2017)

Eligible patients reached age of 18 years with moderate to severe psoriasis (≥ 10% of body surface area involvement), whose disease activity had been stable at least 1 months before entering the study, with adequate evaluation of psoriasis severity as well as data on immunological laboratory markers (number of total lymphocytes, count of CD3+, CD4+, CD8+, CD3+, HLADR cells before and after therapy). Patients had to have discontinued systemic treatments, including: psoralene UVA (PUVA) for the past eight weeks, UVB phototherapy for four weeks, and all topical treatments for two weeks before entering study. Patients with known history of MTX intolerance, photosensitivity, summer form of psoriasis, skin phototype I, oncologic diseases, immunosuppression, alcohol abuse and pregnant or lactating were excluded.

A full body narrowband UVB/UVA standing cabinet was used for a course of phototherapy, the dose of radiation being determined based on the skin phototype guided by the manufacturer's treatment protocols.

The patients were divided into two groups based on received therapy, where Group 1 received MTX 15 mg s/c in regimen once a week for four to six weeks and 311 nm UVB phototherapy with the initial dose 0.1–0.3 J/cm², according to the skin type and protocol of administration — three times a week; increasing the dosage in every next therapy session by 0.1–0.2 J/cm². Patients in Group 2 received MTX monotherapy 2.5 mg two times a day *per os* for five days (total dose in the treatment course 25 mg); intervals three to four days, and four to six treatment courses were allowed in total.

The efficacy of the combination therapy with MTX and 311 nm UVB phototherapy was evaluated using following criteria: significant improvement (PASI decrease by 80%); moderate improvement (PASI decrease by 79–75%); improvement (PASI decrease by 74–50%); no effect (PASI decrease less than 50%); and worsening (remaining negative dynamics or regression of the pathological process).

The PASI (Psoriasis Area and Severity Index) is the most commonly used scoring system for determining the severity, activity, and therapy effectiveness of psoriasis. It is obtained by summing up the main symptoms of psoriasis, including erythema (redness), infiltration, desquamation (scaling), and the percentage of affected skin areas from four anatomical regions: the head, upper trunk, lower trunk, and limbs. This is done using a specially designed mathematical formula (Hartmane *et al.,* 2016).

Additionally, the severity of the disease using the PASI score was assessed before and after the therapy, at the 2nd week of therapy and at the end of therapy: mild to moderate form (< 10% PASI > 10%); moderate severe form (> 10% PASI > 10%); moderately severe to severe form (> 10% PASI 10–20%); and severe form (> 20% PASI > 20%).

Immunoregulatory parameters, such as total lymphocyte count, count of CD3+, CD4+, CD8+, CD3+, HLADR cells in blood, were assessed at baseline and six weeks after the end of therapy; normalisation was defined as lowering of the Th level and increasing concentration of cytotoxic T lymphocytes in blood.

After normality testing, the T test for two dependent samples was used for statistical analysis to compare the changes of PASI, as well immunological parameters before and after the treatment, and the Mann–Whitney U test was used to detect any differences in PASI, as well in above mentioned immunological parameters between therapeutic groups. Statistical analysis was conducted in MS Office Excel 2019.

RESULTS

A total of 211 patients met inclusion criteria; after chart review for information completion 131 patients with moderate to severe form of psoriasis were included in the analysis (Fig. 1).

In total 74 patients were enrolled in Group 1, undergoing 10–24 procedures in the treatment course (mean 17 ± 4.2) with total irradiation dosage 19.9 ± 3.6 J/cm². 57 patients were enrolled in Group 2. Baseline characteristics are given in Table 1.

In the combination therapy group (group 1), mean decrease of PASI at the end of the 2nd week of treatment was by 41%, and in the MTX monotherapy group (Group 2) — by 22%. A lower but more stable decrease of PASI was detected (Fig. 2). At the end of the therapeutic course (4th–6th week), PASI in group 1 reached 5.1 ± 0.2 ($p < 0.01$) and in the second group — 8.8 ± 0.5 ($p < 0.01$). Decrease of PASI in Group 1 was by 81 % on average, and in Group 2 — by 65%.

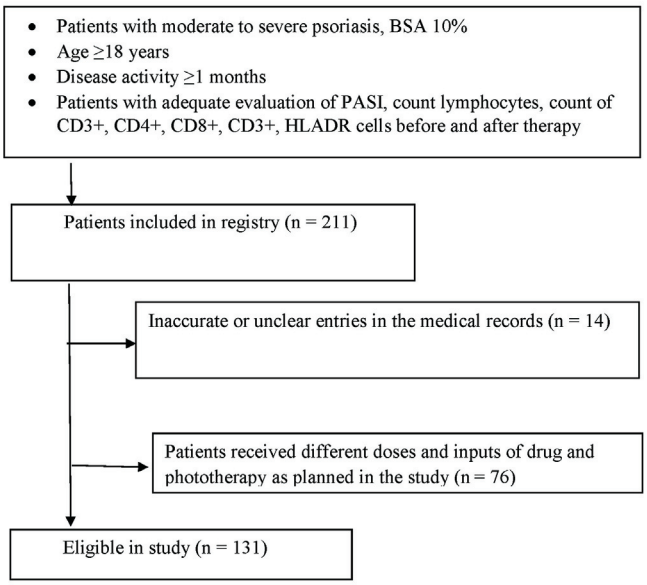

Fig. 1. Screened and excluded patients.

Table 1. Baseline characteristics of the study groups

Characteristics	MTX/NB UVB n = 74	MTX n = 57	*p* value
Age (years)			0.22[t]
Range	23–68	21–64	
Mean ±SD	46.7 ± 4,1	43.3 ± 3,8	
Sex			
Male	38	26	0.77[t]
Female	36	31	
Skin type			0.86[t]
II	62	50	
III	12	7	
Mean duration of disease (years)			0.38*
Range	0.5–26	1–20	
Mean ± SD	9.8 ± 6.3	12.4 ± 7.4	
PASI score at the baseline			
Range	10.2–60.8	10.6–50.1	0.32*
Mean ± SD	26.8 ± 3.9	25.1 ± 4.2	
PASI score after 4–6 weeks of treatment			
Range	0–10.6	3.6–17.9	0.24*
Mean ± SD	5.1 ± 1.1	8.8 ± 1.3	

MTX – methotrexate; NB UVB – narrow band UVB; PASI – Psoriasis Area and Severity Index

[t] Student t test

* Chi Square test

58 (78.4%) patients in Group 1 and 25 (43.8%) patients in Group 2 achieved significant clinical improvement (PASI decrease ≥ 80%). In Group 1, 16 (21.6%) patients and 18 (31.5 %) patients in Group 2 achieved satisfactory improvement (PASI decrease by 79–75%). In Group 2, less rapid improvement was obtained in 14 (24.6%) patients (PASI decrease 74–50%) (see Fig. 3).

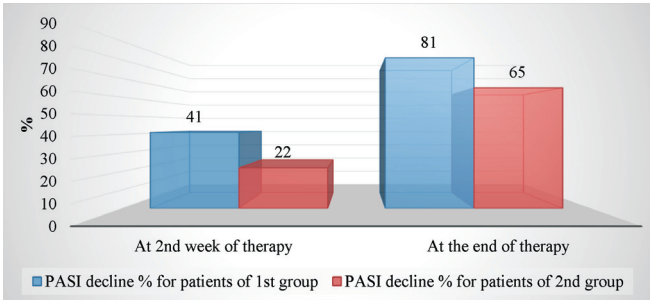

Fig. 2. Changes of PASI in psoriasis patients after combination and MTX monotherapy course.

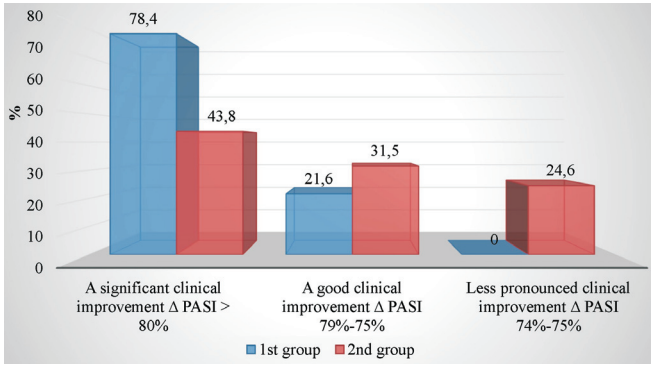

Fig. 3. Data of therapeutic efficacy in comparison of combination treatment method with MTX and 311 nm UVB, and MTX monotherapy.

In Group 2, the therapeutic efficacy was significantly lower than in Group 1 ($p < 0.05$). In Group 1 no side effects or complications were observed, confirming favourable safety of the method. In Group 2, temporary side effects, such as nausea, headache, elevated ALAT in plasma and moderate thrombocytopenia were documented in 13 patients. No treatment was required in these patients since the side effects were mild and self-limiting.

In both groups, before the start of systemic therapy, elevated levels of CD4+, CD8+ were observed in combination with low levels of CD3+ and activated CD3-HLA-DR+ cells in blood serum.

In Group 1, at the end of the treatment course, significant increase of the total lymphocyte count and CD8+ lymphocyte count, and decrease of the CD4+ count were observed ($p < 0.01$). A similar pattern was observed in Group 2, but overall differences before pre- and post- treatment values were smaller and statistical significance was not reached ($p > 0.05$).

The activated CD3-HLA-DR+ count after treatment in both groups did not change significantly and remained in pre-treatment range ($p > 0.05$) (Fig. 4).

DISCUSSION

Multiple treatment modalities are available for treatment of moderate-to-severe psoriasis, including conventional systemic therapy, topical therapy, Nb-UVB therapy, and, most recently, biological therapy. Increasing numbers of biologic

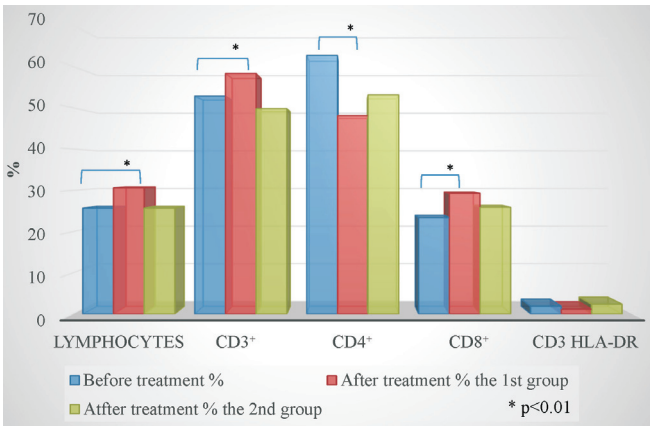

Fig. 4. Immunological parameters in psoriasis patients before and after therapy.

therapies have been developed for moderate-to-severe psoriasis. While there is excellent evidence for new and costly therapies, few trials have investigated the effectiveness and safety of classical therapeutic agents (European S3 guidelines, 2017).

Few studies have been done on the efficacy of combined MTX-UVB phototherapy in different populations and ethnic groups of psoriasis patients. These studies each have different designs, but in all of them, MTX combined with UVB was found to have statistically significant higher therapeutic efficacy and safety than MTX monotherapy (Paul *et al.*, 1982; Lebwohl *et al.,* 2004; Asawanonda and Nateetongrungsak, 2006; Mahajan *et al.,* 2010; Hartmane *et al.,* 2017; Van *et al.*, 2019). Even more, pre-treatment with MTX reduces the dose of UVB radiation and the number of sessions necessary to achieve adequate skin clearing from psoriasis (Paul *et al.*, 1982). Similar results were obtained in our study, verifying efficacy of the combinational therapy approach for the Baltic population.

MTX was prescribed in equal doses in comparable study groups in all previous studies by other authors. One of the main challenges of our study was to collate efficiency and safety of different doses and prescribing routes for MTX in comparable groups, using narrowband UVB phototherapy as additional treatment to subcutaneous MTX. As a result, we found that even lower doses of MTX in combination with UVB phototherapy have higher efficiency and tolerance than when higher dosage was used alone.

Various clinical experiences have suggested that s/c MTX is more effective than oral MTX and may provide significant benefit even in patients in whom oral MTX proved to be inadequate. Mean drug survival (time until discontinuation) for subcutaneous MTX is longer then for the oral form. Switching from oral MTX to subcutaneous MTX significantly reduces gastrointestinal side effects. Particular benefit may be seen in patients, who experienced loss of efficacy after an initial favourable response to oral MTX (Pichlmeier *et* Heuer, 2014; Warren *et al.*, 2017; Attwa *et al.*, 2019).

Studies have shown that the most common side effects of MTX are due to incorrect prescribing and dosing (Wang *et*

al., 2018). It is important that MTX effectiveness is not affected by the duration of psoriasis, PASI, and the body mass index, which significantly expands the range of patients to whom the medicine is to be prescribed (Tournier *et al.,* 2019). These findings encouraged us to consider using s/c MTX in one of the study groups, because the number of phototherapy courses is limited due to its risks for carcinogenesis and photo aging with long-term use. At the same time, MTX in most cases must be prescribed in for the long-term after completing the course of UVB phototherapy to sustain clinical efficacy. Our study provides additional evidence for superior safety of s/c MTX vs oral MTX.

In addition to severe skin forms of psoriasis, a large proportion of Latvian patients also experience psoriatic arthritis (PsA). Therefore, it is often necessary to combine MTX, used in PsA therapy, with narrow band UVB phototherapy. Combined administration of narrow-band UVB phototherapy and MTX may be essential for maintaining a long-term treatment effect. Overall, our study reinforces use of combination therapy with s/c MTX and Nb-UVB in moderate-to-severe psoriasis patients as an effective and safe treatment option before escalation to biological treatment, and is in line with findings from similar studies.

CONCLUSIONS

Combination treatment of moderate and severe psoriasis provides more effective clearance of skin from psoriatic lesions than methotrexate alone. Use of MTX and Nb-UVB simultaneously demonstrates acceptable tolerability and a good safety profile comparable to MTX monotherapy. Combination therapy also has a more powerful influence on immunological parameters, than MTX alone. Our study clearly shows that combined methotrexate and UVB phototherapy can be safely prescribed to psoriasis patients for whom biological drugs are contraindicated or not available. Combined methotrexate and UVB phototherapy can also be used in cases where patients have psoriatic lesions on less than 10% of the skin surface, which are resistant to local therapy and affect the quality of life, but compensation for the purchase of biological drugs in cases of such objectively apparent minor damage is not provided in accordance with the law established in the country.

ETHICS

Rīga Stradiņš University Research Ethics Committee approval was obtained prior to the study (No. 6-1/02/4, 27.02.2020).

CONFLICT OF INTEREST

None.

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RETROSPEKTĪVS KOHORTA PĒTĪJUMS AR FARMAKOLOĢISKĀS ĀRSTĒŠANAS UN FOTOTERAPIJAS EFEKTIVITĀTES UN DROŠĪBAS SALĪDZINĀJUMU VIDĒJI SMAGAS VAI SMAGAS PSORIĀZES PACIENTIEM REĀLĀ VIDĒ

Metotreksāts (MTX) ir viena no sistēmiskās terapijas pirmās izvēles iespējām pacientiem ar vidēji smagu un smagu perēkļveida psoriāzi, un to var kombinēt ar šaura spektra UVB fototerapiju (Nb-UVB). Tomēr šādu kombināciju optimālam ārstēšanas ilgumam lieto reti efektivitātes un terapijas drošības problēmu dēļ. Šī pētījuma mērķis bija novērtēt metotreksāta (MTX) kombinācijas ar mazas devas Nb-UVB un MTX monoterapijas efektivitāti kā arī drošību pacientiem ar vidēji smagu vai smagu perēkļveida psoriāzi reālajā vidē. Tika veikts retrospektīvs psoriāzes pacientu medicīnisko ierakstu apskats un apkopojums.par periodu no 2013. līdz 2019. gadam. Kombinētās terapijas grupa (1. grupa, n = 74) saņēma MTX 10 mg s/c vienreiz nedēļā 4 līdz 6 nedēļas kombinācijā ar 311 nm UVB fototerapiju trīs reizes nedēļā saskaņā ar ādas fototipu un nozīmēšanas protokolu, ārstniecības kursa laikā veicot 10–24 procedūras. Monoterapijas grupa (2. grupa, n = 57) tika ārstēta, pielietojot MTX monoterapiju 2,5 mg divas reizes dienā iekšķīgi piecas dienas nedēļā (kopā 4–6 ārstēšanas kursi). Kombinētās terapijas grupa 2. ārstēšanas nedēļas beigās sasniedza vidējā PASI samazināšanos par 38%, monoterapijas grupa — par 21%. Zemas devas subkutāna MTX un Nb-UVB terapijas kombinācija nodrošina labākus ārstēšanas rezultātus un efektīvāku imūnķīmisko parametru normalizēšanu nekā MTX monoterapija. Šī kombinācija arī uzrādīja labu terapijas panesamību.