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CORRELATION OF IMMUNOLOGICAL AND CLINICAL CHANGES IN PSORIASIS PATIENTS TREATED WITH TUMOUR NECROSIS FACTOR-ALPHA (TNF-α) BLOCKING BIOLOGIC DRUGS: ONE-YEAR DYNAMIC OBSERVATION

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Psoriasis is one of the most common autoimmune dermatoses with a chronic relapsing course. Biologic therapy should be initiated for patients with moderate to severe psoriasis when conventional systemic therapy and phototherapy are ineffective, or their use is limited due to comorbidities. In Latvia, adalimumab is the first choice of biologic drugs for treatment of psoriasis. The correlation between changes in cellular and humoral immunological parameters and clinical signs based on immunological data from psoriasis patients are evaluated in the publication.

Keywords: *TNF-α inhibitors, adalimumab, parameters of cellular and humoral immunity, T cells.*

INTRODUCTION

The modern treatment strategy for psoriasis is based on targeted blockade of inflammatory cytokines or immunocompetent cells with specific inhibitors (Mahi *et al*., 2016; Chiricozzi *et al.*, 2018). Cytokine blocking therapy for psoriasis has several goals:

– elimination of pathological T cells,

– inhibition of T cell activation or migration in tissues,

– immunological correction to regulate cytokine-related effects (increase in Th2-cytokine levels to normalise Th1/Th2 imbalance), and

– binding of inflammatory cytokines (Jackson, 2007; Krueger, 2002).

Tumour necrosis factor alpha (TNF-α) plays an important role in the development of psoriatic inflammation. This cytokine is produced by epidermal keratinocytes, dendritic cells, Th1, Th17, and Th22 lymphocytes. Its main biological effects are:

– increase in the expression of vascular cell adhesion molecule 1, which is involved in the migration of lymphocytes to the inflammatory site;

– activation of lymphocyte and fibroblast proliferation;

– stimulation of leukotriene, prostaglandin, and collagenase synthesis; and

– induction of the synthesis of free oxygen radicals and inhibition of inflammatory cell apoptosis. TNF-α also potentiates the effects of other pathogenic cytokines in psoriatic lesions (Winterfield *et al.*, 2004; Jackson, 2007).

Drugs that block TNF-α are widely used to treat psoriasis (Winterfield *et al.*, 2004; Jackson, 2007; Constantin *et al.*, 2014) due to their demonstrated clinical efficacy in this setting (Jacobi *et al.*, 2006; Elyoussfi *et al.*, 2016; Rendon *et al.*, 2019). In Latvia, adalimumab is the most widely used TNF-α inhibitor for the treatment of psoriasis (Nacionālais Veselības Dienests...).

Adalimumab is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody that blocks TNF-α activity. It

modulates biological responses caused or regulated by TNF (Papp *et al.*, 2011; Poulin *et al.*, Y., 2014; Ronholt *et al.*, 2017; Rendon *et al.*, 2019). It is effective regardless of whether the patient has previously received methotrexate (Strober *et al.*, 2010; Gonzalez *et al.*, 2017; Loos *et al.*, 2018). Adalimumab is well tolerated and causes few adverse reactions (Chiricozzi *et al.*, 2017; Strober *et al.,* 2018; Wy *et al.*, 2018; Leonardi *et al.*, 2019; Sawyer *et al.*, 2019).

Adalimumab administration and dosage in adult psoriasis patients is initiated by subcutaneous injection of 80 mg adalimumab in the first week, followed by 40 mg subcutaneously every other week (Patel *et al.*, 2004; Bongiorno *et al.,* 2008; Vaidya *et al.*, 2015).

The aim of the study was to evaluate and analyse the correlation between changes in cellular and humoral immunological parameters and clinical signs based on immunological data from psoriasis patients.

MATERIALS AND METHODS

The retrospective review was conducted in Rīga, Latvia and was approved by the ethics review board of Rīga Stradiņš University.

A total of 63 patients (21 women and 42 men; aged 18 to 73 years, mean 38.2 ± 15.3 years, with disease history of 2 to 24 years, mean 10.1 ± 5.7) were evaluated. Inclusion criteria were: patients with moderate to severe psoriasis, for whom biologic adalimumab was prescribed based on previous low clinical efficacy or poor tolerability and contraindications to systemic treatment (neotigasone, methotrexate, cyclosporine A) and phototherapy (narrow-spectrum UVB, 311 nm). Exclusion criteria included history of oncological disease, acute and chronic infections including tuberculosis, hepatitis B and C, pregnant women, and breastfeeding women.

Data were collected over one year of adalimumab treatment as dynamic follow-up.

Patients' clinical characteristics were assessed in accordance with the Latvian guidelines for clinical practice in moderate to severe psoriasis (24): PASI — Psoriasis Area and Severity Index, BSA — Body Surface Area, and PGA — Physician's Global Assessment.

In accordance with clinical guidelines, blood samples for immunological testing have to be collected from patients with psoriasis before initiating the biologic therapy, and follow-up testing is performed after one year of therapy application.

Statistical data processing was performed using the IBM SPSS statistics 23 software. For each clinical parameter, changes from baseline value, compared to that after six months and after 12 months, and for immunological parameters after 12 months, were calculated. The T-test for two independent samples was used for comparison. To demonstrate the relationship between clinical and immunological parameters, correlation analysis using the Pearson correlation coefficient was performed. The multi-sample Kolmogorov–Smirnov nonparametric multi-sample test was also used to analyse the effects of previously received treatment methods.

RESULTS

Clinical examination and evaluation of disease severity showed that the mean PASI score was 22.23 ± 0.14, mean BSA index — 16.68 ± 0.44, and mean PGA — 3.0 ± 0.14 before starting treatment (Table 1), thus demonstrating moderate to severe psoriasis. Thirty-two patients previously received systemic treatment with methotrexate, eight patients received cyclosporine A, 11 patients were on synthetic retinoids, and 12 patients had narrow-band ultraviolet B phototherapy. Due to the ineffectiveness or poor tolerability of previous treatment, patients were initiated on adalimumab following the regimen described above.

Table 1. Comparative assessment of psoriasis disease severity with adalimumab as therapy at 6 months (24 weeks) and 12 months (48 weeks)

Parameter	Prior to treatment	After 6 months of treatment (24 weeks)	After 12 months of treatment (48 weeks)
PASI	22.23 ± 0.14	8.09 ± 0.07	3.99 ± 0.02
BSA	16.68 ± 0.44	6.76 ± 0.11	3.30 ± 0.13
PGA	3.00 ± 0.03	1.80 ± 0.01	1.26 ± 0.01

PASI, Psoriasis Area and Severity Index; BSA, Body Surface Area; PGA, Physician's Global Assessment

Evaluation of the same parameters after a six-month treatment course showed the following mean results indicated improvement in disease severity: PASI 8.09 ± 0.07; BSA 6.76 ± 10.11, and PGA 1.80 ± 0.01 (see Table 1). Physical examination at 12 months showed maintained improvement: mean PASI score was 3.99 ± 0.02; mean BSA — 3.30 ± 0.13, mean PGA — 1.26 ± 0.01.

After six months of treatment, mean improvement in PASI score was 63.47% ± 0.43 (max 70.26%, min 52.23%) ($p < 0.0001$), mean improvement in BSA was 57.00% ± 1.64 (max 70.27%, min 20.00%) ($p < 0.0001$), and mean improvement in PGA score was 39.67% ± 0.58 (max 49.72, min 28.10%) ($p < 0.0001$) (Figs. 1, 2, and 3).

During 12 months of adalimumab monotherapy, all 63 patients showed significant improvement of psoriatic lesions, as evidenced by a 81.98% ± 0.15% (max 84.05%, min 79.13%) ($p < 0.0001$) decrease in PASI score, 80.18% ± 0.59 (max 88.24%, min 66.67%) ($p < 0.001$) decrease in BSA and 57.64% ± 0.46 (max 65.63%, min 46.28%) ($p < 0.0001$) decrease in PGA (see Figs. 1, 2, and 3).

All patients underwent cellular and humoral immunological testing before and after treatment with adalimumab. CD3+,

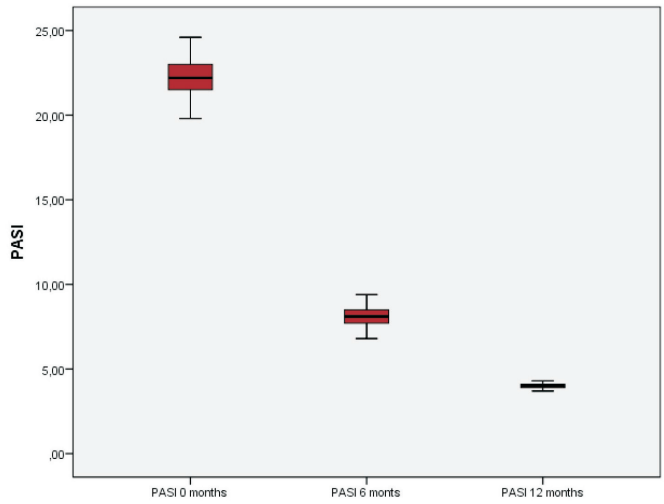

Fig. 1. Changes in PASI (Psoriasis Area and Severity Index) score over 12 months.

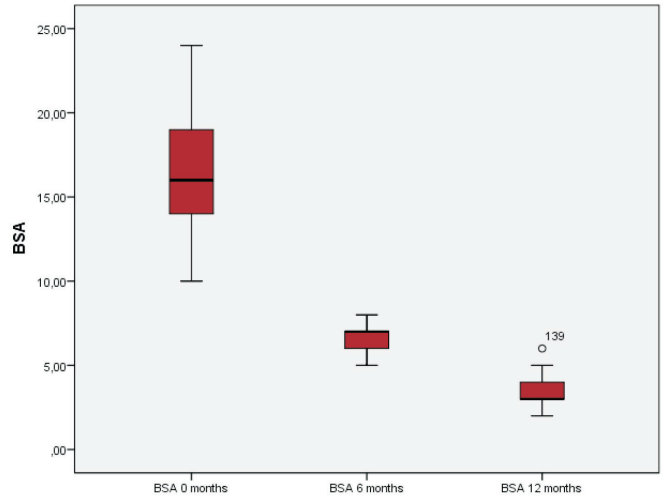

Fig. 2. Changes in Body Surface Area (BSA) over 12 months.

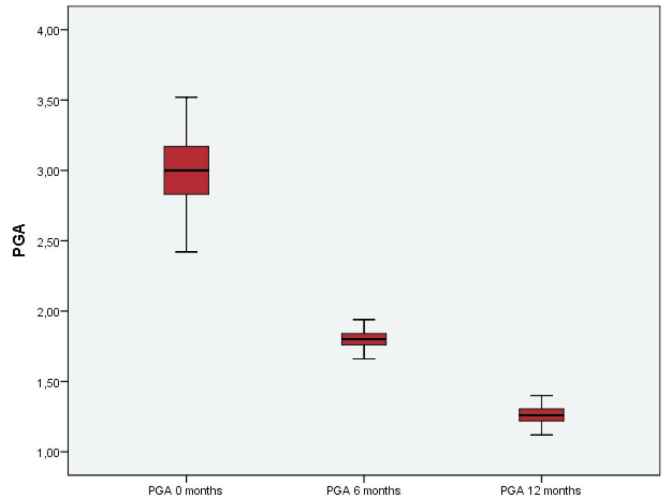

Fig. 3. Changes in Physician's Global Assessment (PGA) over 12 months.

CD4+ and CD8+ subpopulations, CD4/CD8 ratio and levels of immunoglobulins IgA, IgG, IgM, and circulating immune complexes (CIC) IgG, CIC IgA were measured.

Table 2. Changes in cellular immunity parameters in psoriasis patients during adalimumab therapy (M ± m)

Parameter	Normal value, %	Prior to treatment	After treatment
CD3+%	66.8 ± 3.8	59.45 ± 0.11*	$52.91 \pm 0.10^{*+}$
CD4+%	42.9 ± 3.1	65.09 ± 0.17**	$49.19 \pm 0.06^{++}$
CD8+%	28.3 ± 0.7	23.45 ± 0.03*	$32.82 \pm 0.21^{++}$
CD4+/CD8+	1.5 ± 0.3	2.79 ± 0.01*	$1.50 \pm 0.01^{++}$

$^{*}p < 0.05$, $^{**}p < 0.01$ compared to normal values; $^{+}p < 0.05$, $^{++}p < 0.01$ compared to values before treatment with adalimumab

Table 3. Changes in humoral immunity parameters during adalimumab therapy (M ± m)

Parameter	Normal value	Prior to treatment course	After treatment
IgG, g/l	8.4–20.7	13.14 ± 0.21	11.51 ± 0.15
IgA, g/l	0.70–4.10	3.30 ± 0.07	3.14 ± 0.06
IgM, g/l	0.70–3.40	1.21 ± 0.3	1.09 ± 0.30
CIC IgG	0.02–0.14	0.11 ± 0	0.12 ± 0
CIC IgA	0.35–0.75	1.16 ± 0.02	1.15 ± 0.23

CIC (circulating immune complexes) IgA and IgG determined in optical density measurements

Changes in immunological parameters during treatment with adalimumab are summarised in Table 2 and Table 3.

Data in Table 2 show considerable immunological changes, as evidenced by a statistically significant increase in CD4+/CD8+ index compared to the control group and a statistically significant 2-fold increase in T-helper count (CD4+) and decrease or normal level of CD8+ cytotoxic T-lymphocytes, thus balancing the immune response, after 12 months of treatment. In general, after treatment with adalimumab for 12 months, the subpopulation of CD3+ lymphocytes diminished by 12.38 ± 0.29% ($p < 0.0001$), and subpopulation of CD4+ lymphocytes reduced by 24.9% ± 0.22 ($p < 0.0001$), and the subpopulation of CD8+ lymphocytes and CD4+/CD8+ index increased by 39.97% ± 0.99 ($p < 0.0001$) and 91.52% ± 0.05 ($p < 0.0001$), respectively. Immune regulation imbalance prior to treatment was associated with an increased CD4+ cell count, which determines the inflammatory response. A tendency towards normalisation of cellular immunity was observed in psoriasis patients after treatment with adalimumab. The immunoregulatory index reached a normal value or normalised in all patients due to a decrease in CD4+ and increase in CD8+ cell counts (Figs. 4, 5, 6, 7).

A weak correlation tendency with the severity of psoriasis was observed for all indices of cellular immunity: positive correlation for CD4 and CD4/CD8 ratio, and negative for CD3 and CD8 counts (Table 4). During treatment, a moderate positive correlation was found between changes in PASI, BSA and PGA and cellular immunity indices CD4, CD8, CD3, but not the CD4/CD8 ratio Table 5).

The data in Table 6 show changes in humoral immunity parameters in psoriasis patients. Prior to treatment, a small

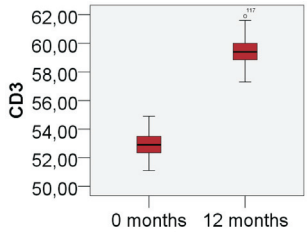

Fig. 4. Changes in CD3 count over.

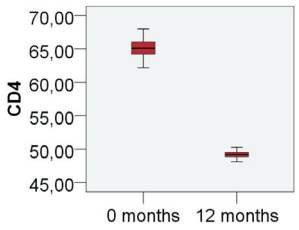

Fig. 5. Changes in CD4 count over.

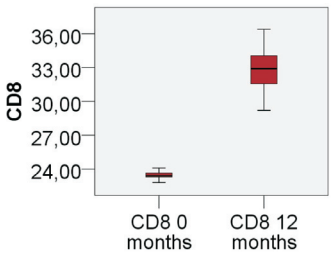

Fig. 6. Changes in CD8 count over.

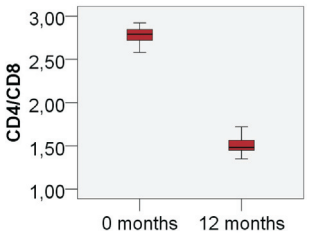

Fig. 7. Changes in CD4/CD8 ratio.

statistically significant increase in IgM and IgG was observed in all patients. At the same time, the IgA level of CIC IgG was within the normal range and did not show a statistically significant change. The CIC IgA level was elevated compared to the normal value, but remained stable after 12 months of treatment (see Tables 3, 6), indicating insignificant dysglobulinaemia.

A decreasing trend in IgA levels was observed in psoriasis patients, demonstrated using a correlation test (see Table 7). The correlation test showed a weak correlation between decrease in psoriasis severity indicators PASI and BSA and IgA. No correlation was found between clinical improvement in psoriasis and other indices of humoral immunity — IgG, IgM, CIC IgG, and CIC IgA (see Table 7)

No clinically relevant laboratory abnormalities were found on clinical and laboratory examination during the observation period. All patients reported good drug tolerability. There were no allergic reactions. Previously received therapy did not affect the effectiveness of the biological drug (p = 0.970).

Table 4. Correlation of psoriasis severity parameters with deviations in cellular immunity parameters

	CD3	CD4	CD8	CD4/CD8
PASI before treatment	–0.370*	0.277**	–0.322*	0.346*
BSA before treatment	–0.252**	0.261**	–0.305**	0.381*
PGA before treatment	–0.349*	0.329*	–0.253**	0.358*
PASI after 12 months of adalimumab therapy	–0.274**	0.199	0.292**	0.306**
BSA after 12 months of adalimumab therapy	–0.219	0.313**	–0.321*	0.359*
PGA after 12 months of adalimumab therapy	–0.326*	0.241	–0.057	0.098

For abbreviations see Table 1. *$p < 0.05$, **$p < 0.01$

Table 5. Correlation of clinical improvement in psoriasis with changes in cellular immunity indices after 12 months of treatment

	CD3	CD4	CD8	CD4/CD8
PASI	0.583*	0.570*	0.565*	0.165
BSA	0.599*	0.588*	0.610*	0.217
PGA	0.576*	0.563*	0.583*	0.198

For abbreviations see Table 1. *$p < 0.05$, **$p < 0.01$

Table 6. Percentage improvement in humoral immunity indices (M ± m)

Parameter	Percentage improvement
IgG, g/l	14.54% ± 1.7 (p = 0.033)
IgA, g/l	3.6% ± 0.067 (p = 0.067)
IgM, g/l	3.70% ± 1.9 (p = 0.002)
CIC IgG	5.83% ± 0.86 (p = 0.066)
CIC IgA	1.05% ± 2.38 (p = 0.765)

CIC, circulating immune complexes

Table 7. Correlation of clinical improvement in psoriasis with changes in cellular immunity indices after 12 months of treatment

	IgG, g/l	IgA, g/l	IgM, g/l	CIC IgG	CIC IgA
PASI	0.029	0.303**	0.021	P0.061	0.046
BSA	0.057	0.294**	0.056	0.003	0.070
PGA	0.109	0.211	0.014	–0.028	0.040

For abbreviations see Table 1. *$p < 0.05$, **$p < 0.01$

DISCUSSION

Despite the advances in modern systemic psoriasis treatments, improvement of disease treatment methods remains and important issue. Particular emphasis should be placed on the safety aspect of treatment, as psoriasis affects not only skin but is a systemic disease associated with significant visceral morbidity as well as psychosocial burden (Puig *et al.,* 2017; Takeshita *et al.*, 2017; Armstrong *et al.*, 2018). Results of many studies suggest psoriatic association with comorbidities, including cardiovascular disease, type 2 diabetes, metabolic syndrome, and adiposity, and may contribute to a further decline in the quality of life and early mortality (Caiazzo *et al.*, 2018). Various comorbid conditions have an important role in the treatment strategy for psoriasis. Conventional systemic therapies are often problematic, as their long-term use can lead to adverse reactions as well as worsening of comorbidities, and require regular laboratory monitoring (Van Luming *et al.*, 2011; Hartmane *et al.,* 2016). Treatment should aim not only at preventing inflammation but also prolonging the duration of remission and lowering the burden of comorbid conditions (Gisondi *et al.*, 2013). Based on international and local guidelines for psoriasis treatment, the main systemic therapies for moderate to severe psoriasis are synthetic retinoids, cytostatic drugs, and biologics. However, long-term use is associated with significant adverse reactions. For example, cyclosporine exhibits hepatic toxicity and nephrotoxicity, and may contribute to the development of arterial hypertension, impaired glucose tolerance, and promote dyslipidaemia. Therefore, cyclosporine is contraindicated in patients with metabolic syndrome as well as those with impaired renal function. Acitretin has hepatotoxic effects and may cause or worsen hypercholesterolaemia or hypertriglyceridemia.

Methotrexate and acitretin are also teratogenic and may be used only with great caution in women of childbearing potential. Methotrexate is also contraindicated in patients with alcohol use disorder or chronic hepatic impairment (Gisondi *et al.*, 2013a; 2013b; Zweegers *et al.*, 2016).

Monoclonal antibody preparations are better tolerated during long-term treatment. The main concern with the use of biologics is increased risk of infections. These agents should not be used in psoriasis patients with concomitant multiple sclerosis or another demyelinating disease. In most cases, they are not used during pregnancy and lactation and are not recommended for patients with congestive heart failure (Nast *et al.*, 2012).

Numerous clinical trials have demonstrated the ability of adalimumab not only to effectively prevent inflammation and significantly reduce the amount of immune cells infiltrating the dermis and epidermis in psoriasis, but it also exhibits a favourable safety profile and good tolerability (Papp *et al.*, 2013; Gniadecki *et al.*, 2018; Talamonti *et al.*, 2018). However, a comprehensive evaluation of the efficacy of adalimumab by linking skin clinical improvement to cellular and humoral immune parameters has not been performed previously. Therefore, the results obtained in our study can be considered innovative. Some publications only analyse the changes in the phenotype of cells involved in the pathogenesis of psoriasis and the changes in various antibodies and their immune complexes during psoriasis (Laurent *et al*., 1981; Ozturk *et al*., 2001; Langewouters *et al*., 2007).

Our study assessed the levels of PASI, BSA, PGA, as well as summarised changes of several immunological parameters during the treatment with adalimumab, which are of importance in pathogenesis of psoriasis, like CD4, CD8, CD3 CD4 / CD8 ratio, IgM, IgG, IgA, CIC IgM, and CIC IgA. Changes in the number and ratio of CD4 to CD8 lymphocytes are the essential prerequisites for pathogenetic development of psoriasis. Quantitative and qualitative deviations of various antibodies, mainly their immune complexes, are observed with the progression of chronic systemic inflammation by psoriasis (Oztürk *et al*., 2001; Langewouters *et al*., 2007; Chiricozzi *et al*., 2018).

We recommend these parameters to evaluate and predict the efficacy of adalimumab and other biologics. The effectiveness of biologics is most often affected by the formation of antidrug antibodies (ADA). It should be noted that ADA are not always the cause of drug neutralisation. They also cause the side effects of biologics, an inflammatory reaction caused by ADA-induced activation of immune cells by the MHC II molecule. Thus, the determination of ADA in the blood to predict the loss of efficacy of a biological medicinal product in a timely manner may be inaccurate.

Adalimumab's safety profile and low risk of drug interactions allows it to be used in elderly psoriasis patients, as well as in individuals with associated cardiovascular disease, metabolic syndrome and diabetes mellitus (Menter *et al.*, 2015; Nast *et al.*, 2015).

In the pathogenesis of psoriasis, the circulation of other inflammatory molecules in tissues and organ systems increases due to the central axis cytokines IL23, IL17, TNF-α, and IL12. The consequences are chronic inflammation throughout the body, resulting in a series of comorbidities characteristic in psoriasis, which include metabolic syndrome, hypertension, bronchial asthma, and other diseases. In our study, patients with comorbidities specific to psoriasis were included in the actual psoriasis population. Given that these comorbidities share a common mechanism of pathogenesis with immunological processes in the skin, we assume that the correlation data were not unaffected in this way.

The weak correlation between psoriasis severity and abnormalities in cellular immunity may be a consequence of the migration of inflammatory cells from the blood to the lesion site. Langewouters *et al.* (2007) demonstrated that each immunological cell subphenotype had a different intensity of influx from blood to the psoriatic lesion, which, moreover, varied with different degrees of psoriasis severity. Similarly, to our study, Langewouters *et al.* (2007) deny the correlation of the CD4 / CD8 ratio with the severity of psoriasis.

Ozturk *et al.* (2009) reported elevated blood IgA and IgG levels in psoriasis patients. In our study, a decrease in IgA, IgG, and IgM levels was observed. Although the downward trend in IgA levels was not statistically significant, the correlation test showed a weak association between IGA and the severity of psoriasis.

Laurent *et al.* (1981) found an association between elevated levels of circulating immune complexes and psoriatic arthritis, but not with the severity of psoriasis. This explains why our study did not show any effect on the clinical improvement of psoriasis with respect to circulating immune complexes.

The results of our study show that adalimumab promotes reduction of skin inflammation in psoriasis. Prior to treatment, all patients showed an increased level of IgA, indicating marked activity of the psoriatic process in the skin and, according to the literature, in the synovial membranes in psoriatic arthritis (Laurent *et al.*, 1981; Toruniowa, 1992; Thomas *et al.*, 2019).

Adalimumab is an effective treatment for moderate to severe psoriasis. It has been shown to be convenient and safe for the patient, meaning that dynamic observation periods may be longer than with conventional systemic therapy and there is low risk of target organ toxicity, when following clinical guidelines for dynamic patient monitoring.

CONCLUSIONS

1. The study demonstrates the pathogenetic efficacy of adalimumab therapy in patients with moderate to severe psoriasis for whom previous treatments with conventional systemic therapy and phototherapy have failed.

2. Patients with moderate to severe psoriasis were found to have impaired cellular and humoral immunity, characterised by elevated CIC IgA levels, decreased total T-lymphocyte counts and an abnormal CD4+/CD8+ ratio with T-helper cell predominance.

3. Adalimumab therapy resulted in immunological response changes: normalisation or a trend towards normalisation of cellular and humoral immunity parameters with clinical improvement or complete regression of clinical symptoms.

4. Adalimumab has systemic immunomodulatory effects in patients with moderate to severe psoriasis.

5. The use of adalimumab in patients with moderate to severe psoriasis shows relatively rapid clinical improvement, a significant reduction in the risk of adverse reactions, and allows long-term dynamic monitoring, significantly improving the patients' quality of life.

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IMUNOLOĢISKO UN KLĪNISKO PĀRMAIŅU KORELĀCIJA PSORIĀZES PACIENTIEM, KURUS ĀRSTĒ AR AUDZĒJA NEKROZES FAKTORU ALFA (TNF-α) BLOĶĒJOŠIEM BIOLOĢISKIEM MEDIKAMENTIEM: DINAMISKI NOVĒROJUMI VIENU GADU

Psoriāze ir viena no visbiežākajām autoimūnām dermatozēm, kas norit ar hronisku recidivējošu gaitu. Pacientiem ar mērenu vai smagu psoriāzi, kam parastā sistēmiskā terapija un fototerapija ir neefektīva, vai tās lietošana ir ierobežota blakuslimību dēļ, jāuzsāk terapija ar bioloģiskajiem medikamnetiem.. Latvijā *adalimumab* ir pirmās izvēles bioloģiskais medikaments psoriāzes ārstēšanai. Publikācijā tiek vērtēta saistība starp šūnu un humorālo imunoloģisko parametru izmaiņām un klīniskajām pazīmēm, kas balstītas uz psoriāzes slimnieku imunoloģiskiem datiem.