BIOETHICAL APPROACH TO ESTIMATION OF PHARMACOEPIDEMIOLOGICAL AND PHARMACOECONOMIC ASPECTS OF PSORIASIS TREATMENT

Samarina EI, Lileeva EG ✉, Rybachkova JV

Yaroslavl State Medical University, Yaroslavl, Russia

Bioethical approach to determine the feasibility of using medicines involves systemic analysis of pharmacoepidemiological and pharmacoeconomic aspects of treatment, especially while treating the most common and chronic diseases. Psoriasis is the most common disease of the skin and subcutaneous tissue, accounting for 15% of cases. The rate of psoriatic complications constitutes 6–42%. Skin lesions, psoriatic arthritis, cardiovascular diseases, metabolic syndrome, inflammatory intestinal diseases, mental disorders and malignant lesions produce a great effect on health, duration and quality of life, and result in early loss of labor capacity and disability of patients. So, it is important to study effectiveness and safety of systemic medicines in patients with severe and moderate-to-severe disease and perform subsequent analysis of possible use and comparison of the effectiveness of various combinations. Most affordable but ineffective medicines commonly cause real growth of further expenses on treatment, and postpone administration of more effective, though much more expensive medicines. Economic aspects of rational use of healthcare resources are becoming increasingly important whereas pharmacoeconomic values are crucial while selecting a treatment strategy.

Keywords: psoriasis, pharmacoeconomics, genetically engineered biological drugs, NNT (number needed to treat), CpR (cost per responder), methotrexate

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✉ **Correspondence should be addressed:** Elena G. Lileeva
Revolutsionnaya Str., bld. 5, Yaroslavl, 150000, Russia; elileeva2006@yandex.ru

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ФАРМАКОЭПИДЕМИОЛОГИЧЕСКИЕ И ФАРМАКОЭКОНОМИЧЕСКИЕ АСПЕКТЫ ЛЕЧЕНИЯ ПСОРИАЗА

Е. И. Самарина, Е. Г. Лилеева ✉, Ю. В. Рыбачкова

Ярославский государственный медицинский университет, Ярославль, Россия

Среди болезней кожи и подкожной клетчатки псориаз является самым распространенным заболеванием, на долю которого приходится 15%. Частота псориатических осложнений при псориазе составляет 6% — 42%. Поражения кожи, псориатический артрит, сердечно-сосудистые заболевания, метаболический синдром, воспалительные заболевания кишечника, психические расстройства и злокачественные новообразования оказывают большое влияние на состояние здоровья, продолжительность и качество жизни, приводят к преждевременной потере трудоспособности и инвалидизации больных. Поэтому огромное значение приобретают клинико-экономические аспекты лечения бляшечного псориаза и его сопутствующих проявлений, а именно оценка расходов пациентов и их ближайших родственников, инвалидизация пациентов и затраты на амбулаторное и стационарное лечение.

Ключевые слова: псориаз, фармакоэкономика, генно-инженерные биологические препараты, NNT (number needed to treat), CpR (cost per responder), метотрексат

Вклад авторов: авторами проведен обзор литературных данных по тематике исследования в области фармакоэпидемиологических и фармакоэкономических аспектов лечения псориаза. Авторы внесли равный вклад в написание статьи.

✉ **Для корреспонденции:** Елена Георгиевна Лилеева
ул. Революционная, д. 5, г. Ярославль, 150000, Россия; elileeva2006@yandex.ru

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Psoriasis is a systemic immune-mediated multifactorial disease, which occupies an important position in the structure of skin diseases and is associated with a dominant value in the development of genetic factors characterized by an accelerated proliferation of keratinocytes and their disturbed differentiation, and imbalance between pro- and anti-inflammatory cytokines with frequent abnormal changes of the locomotor apparatus [1, 2].

Psoriasis is a common skin and subcutaneous disease. The proportion of patients with psoriasis reaches 15% [3]. According to the WHO, 125 million people around the globe suffer from the disease [4]. In 2018, prevalence of psoriasis in Russia was 0.24% (356,030 people) [1]. In 2018, diseases of skin and subcutaneous tissue rank 4th in the structure of morbidity in the Russian Federation [3].

The rate of psoriatic complications constitutes 6–42% [5]. Severe and moderate-to-severe diseases are found in 20% and 30% of cases, respectively [6]. Skin lesions, psoriatic arthritis, cardiovascular diseases, metabolic syndrome, inflammatory intestinal diseases, mental disorders and malignant lesions produce a great effect on health, duration and quality of life, and result in early loss of labor capacity and disability of patients. Thus, clinical and economic aspects of treatment of plaque psoriasis and its respective complications, namely, assessment of expenses borne by patients and closest relatives, disability of patients and expenses on outpatient and inpatient treatment are of significant importance.

The problems of plaque psoriasis therapy are associated with a delayed complex approach of prescribing drugs,

correction of many concomitant diseases and low adherence to treatment. Quality of life and neurological anxiety-depressive disorders are crucial while assessing health, effectiveness and safety of drug-induced therapy in long-term treatment of chronic diseases, particularly, plaque psoriasis combined with psoriatic arthritis. The last ones are taken as factors that do not only accompany the somatic well-being but also worsen the course of diseases and quality of life [7]. Thus, a complex analysis of drug-induced therapy obtained by patients with plaque psoriasis and concomitant psoriatic arthritis seems to be a pressing issue, solution of which promotes a favorable course of the disease taking into account the clinical and economic constituent.

Control over the process of rendering medical services does not guarantee success. Clinical research only without generalization of results fail to effectively contribute to the use of healthcare resources due to a physical impossibility to comprehend enormous amounts of information. As no work associated with clinical and economic studies is coordinated and carefully targeted, they are all separated now and devoted to various narrow topics such as the use of a certain drug in a certain dosage within a certain group of patients with various confounding factors.

Moreover, significantly different methods described in various works hamper result generalization as the medicines are used in a variety of dosages and duration of observation of patients varies as well. To sum up, the results of different works are incomparable and the volume of information is significantly increased. Thus, neither attending physician nor administrator has enough time to trace and estimate the available level of evidence regarding treatment methods even if it was filtered out using meta-analyses as the data of direct comparative studies are limited. Special mechanisms that would allow to supply doctors with reliable information about the methods with proven effectiveness and safety are required [8].

Clinical recommendations, which were last revised in 2023, were considered as a required tool of managing patients with plaque psoriasis. They were a means that support taking clinical solutions or mechanism of regulation of expenses as they described therapy priority and linearity.

Almost 70–80% of patients have mild psoriasis, which can be treated with local therapy [7]. Mild psoriasis is determined taking into account 10% of the affected body surface area (BSA), Psoriasis Area and Severity Index (PASI) (10 scores), and Dermatological Quality of Life Index (DQLI). Psoriasis is classified as moderate and severe if BSA >10% or PASI >10 and DLQI >10 scores and if it corresponds to one or several increasing criteria such as distinct affection of visible areas, scalp, genitals, palms and soles, psoriasis of nails, itching and stable plaques.

According to advanced guidelines that have been revised during the last ten years, therapy goals included skin cleansing by 90–100% as compared with the initial value (PASI 90, PASI 100) (National Psoriasis Foundation) [9] and global estimation by an investigator at the level of 0–1 scores (PGA 0–1) (Societe Francaise de Dermatologie) [10].

The latest recommendations of the Japanese Association of Dermatologists of 2020 include the DLQI (0/1 scores) [10].

The latest clinical recommendations on psoriasis as of 2023 contain a clear algorithm of selecting a therapeutic direction (fig.). In case of limited eruptions, external therapy is applied, whereas systemic therapy is used in extensive eruptions.

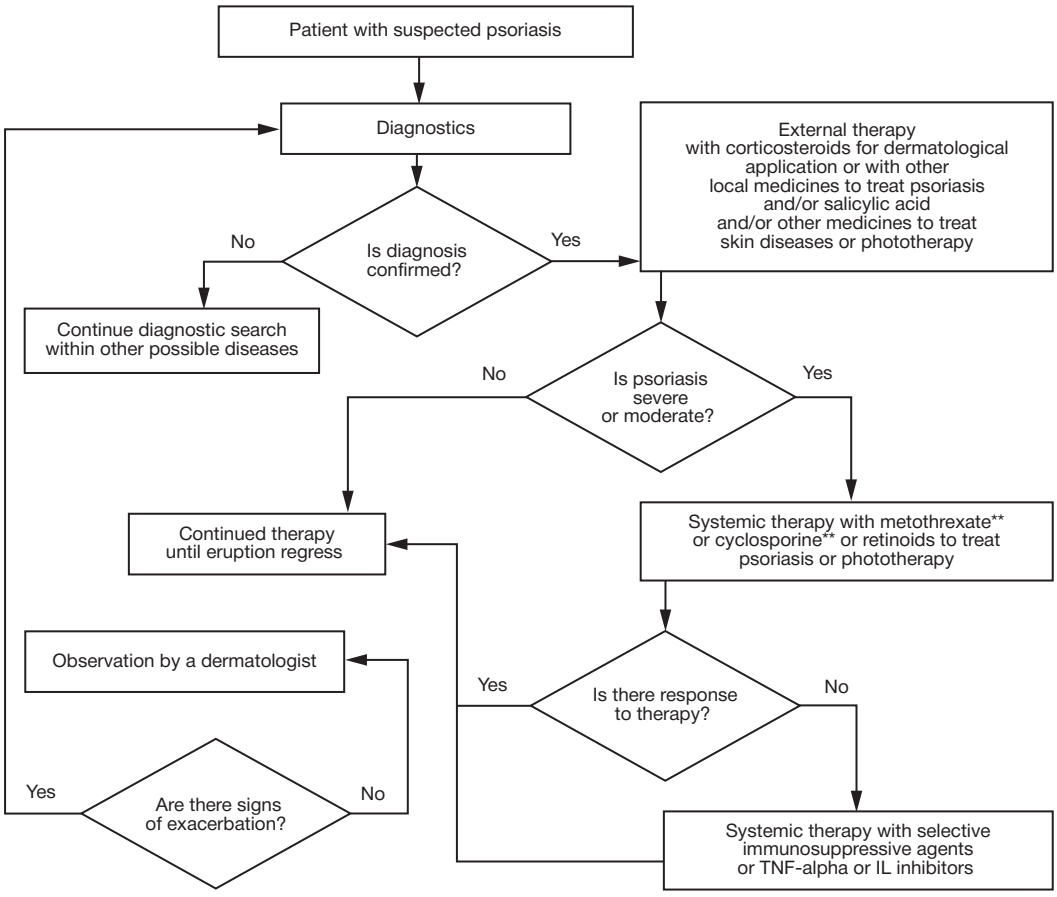

Fig. Algorithm of managing patients with psoriasis as per the latest clinical recommendations (2023).

Systemic therapy includes systemic immunosuppressive agents (including systemic photochemotherapy), Janus kinase inhibitors and genetically engineered biological agents. Systemic glucocorticoids are used in some conditions (generalized pustular psoriasis, psoriatic erythroderma).

In accordance with clinical recommendations, moderate-to-severe and severe psoriasis is treated with the following agents [1, 11]:

- systemic immunosuppressive agents (cyclosporine, methotrexate, acitretin, apremilast, systemic photochemotherapy);
- Janus kinase inhibitors (Tofacitinibum);
- genetically engineered biological agents such as TNF inhibitors (Infliximab, adalimumab, etanercept, certolizumab pegol), IL-12/23 ustekinumab, IL-17 (secukinumab, ixekizumab, netakimab), IL-23 (guselkumab, risankizumab).

Burden of comorbidities is growing during the life of a patient with psoriasis. The issue of accumulated influence of a disease on a patient's life and health is being actively discussed. The volume of accumulated burden results in stable psychosocial and personal disturbances. It makes human health irreversibly altered. An earlier diagnostics of psoriasis subtype and timely beginning of pharmacotherapy with properly selected medicines can slow disease progression and prevent social isolation of patients. It should be noted that modern genetically engineered drugs have an ethical advantage as patients can get acquainted with open-source data beforehand and expect clinical effectiveness to be obtained in quite a short time as compared with standard therapy, for instance, with methotrexate, ciclosporin and retinoids. On the other hand, it does not mean that a patient with burdened disease progression independently solves complex clinical and ethical issues and estimates benefit, harm, and safety of therapy suggested by a doctor. All clinicians are advised to act in accordance with clinical recommendations without skipping the graduation and priority of therapy. Progress in the development and registration of novel short-acting drugs raises numerous ethical issues. The issues are about how to balance and protect this group of patients from possible risks associated with increased emotional dissatisfaction with consistent therapy when genetically engineered drugs represent the last hope. Anonymity and confidentiality belong to other ethical issues of treating patients with psoriasis. Many employed patients prefer not to inform the employer of their disease. This makes them search for the most effective methods of treatment independently and discuss such an administration with the treating physician ignoring the legally adopted step therapy.

SYSTEMIC IMMUNOSUPPRESSIVE AGENTS

Methotrexate is considered as a highly effective agent to treat common psoriasis, psoriatic erythroderma, pustulous and arthropathic psoriasis.

Zilberberg NV and Kokhan MM analyzed their experience of treating psoriasis with methotrexate, a golden standard of systemic therapy, administered by intramuscular and subcutaneous injections [12]. The submitted results of using methotrexate in therapy of patients with moderate-to-severe and severe psoriasis administered by subcutaneous injections as compared with intramuscular injections demonstrated a highly effective course of treating psoriasis and psoriatic arthritis with methotrexate. The data regarding a higher safety, a more significant positive influence on life quality, better tolerance and a longer remission were achieved within a group of patients administered subcutaneous injections of methotrexate.

Methotrexate (4-amino-10-methyl-folic acid) belongs to a group of cytostatic agents and is an antagonist of folic acid. In the clinical setting, the preparations are combined. Methotrexate competitively inhibits dihydrofolate reductase and some pholate dependent enzymes resulting in suppressed synthesis of nucleic acids and, ultimately, DNA and RNA synthesis suppression. Meanwhile, nucleic acid synthesis is suppressed in every dividing cell of gastrointestinal tract, liver, immune system and skin [13]. Methotrexate inhibits production of inflammation mediators such as leukotrienes, TNF-α, IL-1β and adhesion molecules (E-selectine and VCAM-1) and prevents adhesion of white cells to the vascular endothelium.

According to literature, methotrexate therapy decreased the percentage of TNF-positive CD4+ T cells in the peripheral blood of patients with rheumatic disease but increased the number of IL-10-positive T-cells [12, 13].

According to the latest clinical recommendations, patients with plaque psoriasis are administered methotrexate if systemic therapy is indicated (in case of resistance to the conducted external therapy and in common moderate or severe rashes) [14].

At the same time, according to Gallyamov YuA and Asokov AV, long-term therapy with methotrexate allows to claim its effectiveness in patients with psoriasis and psoriatic arthritis. However, the possibility of adverse events including hepatoxicity, anemia and neutropenia, gastrointestinal events (nausea, vomiting, stomatitis, loss of appetites) is not excluded. This decreases therapy compliance and limits its use [15].

Cyclosporine is one of the best-known drugs to treat psoriasis, which produces not only an anti-inflammatory but also a cytostatic effect. The drug has a narrow therapeutic window. Regular control of plasma creatinine is required as a nephrotoxic effect, blood pressure rise, changes in the level of potassium, uric acid, bilirubin, transaminase, and lipid profile are possible. The drug should be withdrawn on a constant basis. Due to cytostatic and immunosuppressive effects, treatment with cyclosporine increases the risk of lymphoproliferative diseases and other malignant lesions, especially those of the skin [15].

JANUS KINASE INHIBITORS

Tofacitinibum was the first Janus kinase inhibitor registered for treatment of plaque psoriasis ad psoriatic arthritis (PsA). Effectiveness and safety of tofacitinibum at doses of 5 and 10 mg BID for PsA treatment was studied in two placebo-controlled studies in 710 patients with no response to standard DMARDs (ORAL Broaden) and combination therapy with DMARDs and TNF-α inhibitors (ORAL Beyond) [16]. In the both studies, Janus kinase inhibitors were combined with DMARDs and methotrexate, in particular. During the ORAL Broaden study, a group of patients obtained adalimumab. In 3 months, the rate of response by AKP20 criteria was significantly higher in the tofacitinibum group (50.0–53.0%) as compared to placebo (28.0%). Similar results were obtained when the response was analyzed by AKP50 and AKP70 criteria. Moreover, treatment with tofacitinibum resulted in a more significant improvement of the functional activity of patients assessed based on HAQ-DI and a decreased number of tender and swollen joints. Advantage of tofacitinibum over placebo was recorded when effectiveness of psoriasis, enthesitis, dactylitis and spondylitis (BASDAI) treatment was assessed. In the ORAL Broaden study, no significant difference was found for tofacitinibum as compared with adalimumab.

GENETICALLY ENGINEERED BIOLOGICAL AGENTS (GEBAS)

GEBAs are third-line agents for patients with psoriasis. Genetically engineered biological therapy is indicated to patients with psoriasis and psoriatic arthritis in the following cases:

1) in the presence of comorbid and concomitant diseases that make it impossible to use a standard systemic immunosuppressive therapy;
2) in the presence of active progressive psoriatic arthritis with factors of unfavorable prognosis, high activity spondylitis combined with functional disturbances and ineffective standard therapy of NSAIDs at therapeutic doses; polyarthritis with joint erosion, functional disturbances if standard therapy is not effective; multiple enthesitis and dactylitis with functional disturbances refractory to standard therapy;
3) in certain (problematic) location of psoriatic elements (exposed skin, genitals, palms and soles; pronounced psoriatic onychodystrophy) and a significant decrease of life quality (DLQI > 15) [12].

Nowadays, TNF-α inhibitors, interleukin 17 inhibitors, interleukin 12/23 inhibitors, and interleukin 23 inhibitors are approved to treat moderate to severe psoriasis. Low-molecular inhibitors such as apremilast and deucravacitinib are also approved to treat psoriasis [1]. Nevertheless, it is not clear yet how systemic agents to treat psoriasis influence concomitant diseases by changing the systemic inflammation.

Data of clinical trials of safety and effectiveness of biological preparations and low-molecular inhibitors are important for a personalized approach to treatment of patients with psoriasis. Notably, treatment with IL-17 inhibitors is associated with new onset or exacerbation of an inflammatory bowel disease.

Nevertheless, more caution should be taken while using TNF-α inhibitors in patients with psoriasis and concomitant congestive cardiac failure, disseminated sclerosis and malignant lesions. Apremilast can result in the loss of weight as an adverse effect and also produce some positive metabolic effect [4].

It is necessary to consult a TB specialist prior to administration of GEBAs and during therapy with GEBAs. Reactivation of mycobacterial infection with TB of lungs and other organs is possible against the background of therapy with TNF-α or IL inhibitors as immunosuppressive action of drugs and activation of mycobacterial infection with a higher risk as compared with TNF-α inhibitors can be recorded [17–22].

The most commonly administered drugs include the ones inhibiting effectory interleukins 17 such as Netakimab, Secukinumab, Ixekizumab with a similar mechanism of action and drugs inhibiting regulatory IL-23, in particular, Guselkumab and Risankizumab.

Secukinumab is a human monoclonal IgG1k antibody that has been developed to target and block the actions of IL-17A. This is how its binding with receptors and stimulated expression of pro-inflammatory genes are prevented [19].

The most common adverse events while taking secukinumab included infections of the upper respiratory tracts, oral herpes, ringworm of foot, rhinitis, and diarrhea [23].

Guselkumab is intended to treat moderate-to-severe and severe plaque psoriasis in adults who are receiving systemic therapy. Guselkumab as monotherapy and combined with methotrexate is indicated to treat active psoriatic arthritis in adults with insufficient response or intolerance of previous therapy with basic anti-inflammatory agents. In psoriasis, guselkumab is generally administered as 100 mg subcutaneous injections at Week 0, Week 4, then every 8 weeks.

Risankizumab is a fully human IgG monoclonal antibody that binds with high affinity to the p19 sub-unit of IL-23. In phase 3 clinical psoriasis trials, neither of 72 participants with latent TB who were administered Risankizumab and obtained proper preventive TB therapy developed an active form of TB within 61 weeks of follow-up against therapy with risankizumab [24]. None of 31 patients with latent TB involved in the IMMHANCE study who failed to obtain preventive TB treatment developed active TB within 55 weeks of therapy with Risankizumab [24]. Up to 16 weeks safety of risankizumab was analyzed in the integrated data from the placebo- or active-comparator studies. Serious adverse events occurred in 2.4% of patients with Risankizumab as compared with 4.0% in placebo group and 5.0% in the group of ustekinumab.

Anti-TB therapy should be considered prior to initiating guselkumab in patients with a past history of latent or active TB in whom an adequate course of treatment is not confirmed [25]. No active form of TB developed within a 43-week observational period of clinical studies involving 105 subjects with latent TB who were administered guselkumab and concomitant preventive therapy.

PHARMACOECONOMIC ANALYSIS OF PSORIASIS THERAPY

Active development of biotechnologies provided a rather wide access to biological agents for psoriasis treatment. Thus, an optimal choice of therapy acquires a great importance.

In the works of Bakuleva AL and Mladova VV, effectiveness and safety of biological and synthetic medicinal agents were accessed based on NMA (network-meta-analysis) methodology [26]. The goal of this study was to determine the value of NNT (number needed to treat) and respective CpR (cost per responder) value based on PASI 75/90 criteria following 12 weeks and one year of therapy for every targeted drug such as adalimumab, apremilast, ixekizumab, guselkumab, infliximab, netakimab, secukinumab, tofacitinib, ustekinumab, certolizumab pegol, tofacitinib and etanercept.

It should be noted that NNT index has been proposed as an effect indicating a number of patients who should be treated to achieve an additional expected outcome, whether a positive or a negative, as compared with another drug within the reviewed interval of time. CpR characterizes expenses on the same response to therapy within the reviewed interval and represents the result of effect multiplied by the cost of therapy with any medicinal agent in one patient.

The analysis of NNT and CpR indexes has shown that netakimab is the most economically effective therapy option in moderate-to-severe and severe plaque psoriasis as assessed by PASI 75/90 both in the short-term 12-week, and long-term 52-week periods [26].

In the scientific work by Rudakova AV and Tolkachyova DG, netakimab has shown a higher clinical and economic effectiveness as compared with other GEBAs. According to analytics, the use of netakimab in the therapeutic practice of psoriatic arthritis will decrease the load onto the healthcare budget by 21.1% during 3 years. And even if the healthcare system budget is preserved, a number of patients who can be cured during 3 years will be increased by 26.7% [27].

According to research data of Nasonov VA Research Institute of Rheumatology, economic advantages of secukinumab are presented as compared with TNF inhibitors and ustekinumab [28].

The goal of another research paper was to study possible localization of manufacture of drugs based on monoclonal antibodies in the lyophilized form. The market of medicines based on monoclonal antibodies in the lyophilic form manufactured in the Russian Federation demonstrated a significant growth from 2016 to 2020. In money term, the production increased from 1,997 to 7,589 bln RUB accounting for 20% and 45% respectively. It was established during the analysis that the period of patent protection of such international nonproprietary names as basiliximab, infliximab, omalizumab, and trastuzumab has expired. Researchers also analyzed the market structure of drugs based on monoclonal antibodies. It was found out that all medicines based on monoclonal antibodies are included into the list of vital and essential drugs the price formation of which is regulated by the country. The absolute volume of state financing of medicines based on monoclonal antibodies increased from 9,928 to 16,801 bln RUB from 2016 to 2020 [29]. One of ultimate observations of researchers from Saint-Petersburg Chemical and Pharmaceutical University of the Ministry of Health of Russia was to increase sales of localized drugs based on monoclonal antibodies in the lyophilic form in natural and money terms in a significant remaining localization potential [29].

In accordance with the results of a systematic review of effectiveness of targeted agents in the therapy of adults with severe-to-moderate and severe vulgar psoriasis in Russia by PASI 75, i.e. skin cleansing by 75% as compared with the initial result, risankizumab and ixekizumab were significantly more superior to all TNF-α inhibitors (infliximab, adalimumab and etanercept), small molecules (tofacitinib, apremilast) and IL-12/23 inhibitor ustekinumab, whereas netakimab and guselkumab had a comparable effectiveness with infliximab and were superior to the remaining drugs [30]. All TNF-α inhibitors had comparable effectiveness.

While using guselkumab, ixekizumab, infliximab, netakimab, risankizumab and secukinumab, at least two or no more than three patients by PASI 90 should be treated to achieve the same response with PASI 75 (along the upper border of 95% credible interval). Just like in the majority of previously published studies, the use of netakimab allowed for less expenses on achievement of the same response both during 12 weeks, and during one year of therapy.

Based on the results of updated network meta-analysis, IL-17 netakimab, ixekizumab, IL-23 guselkumab and risankizumab demonstrated high effectiveness as compared to other target drugs to treat vulgar psoriasis both by the percentage of patients who achieved PASI 75 and by other outcomes (PASI 90/100, PGA/IGA 0/1, DLQI) following 12 weeks of therapy [30]. Meanwhile, netakimab demonstrated a smaller CpR index by PASI 75/90 following 12 and 52 weeks of therapy [30].

CONCLUSION

The urgency of pharmacotherapy of plaque psoriasis is due to a necessary constantly improved approaches to the rational use of medicines in accordance with clinical recommendations and WHO recommendations as a main component of the national drug-induced policy. Rational pharmacotherapy produces a significant effect not only on a patient's life quality, but also on treatment cost including therapy-related expenses borne by a patient, and the state. As far as novel genetically engineered medicines acting on different targets of psoriasis go, there are no convincing data that confirm effectiveness of using various classes of systemic agents in patients with plaque psoriasis. Economic aspects of rational use of healthcare resources are becoming increasingly important whereas pharmacoeconomic values are crucial while selecting a treatment strategy. Use of most affordable but ineffective medicines commonly causes real growth of further expenses on treatment, and postpones administration of more effective though much more expensive medicines.

Thus, examination of clinical and economic aspects of psoriasis therapy is the most important constituent while providing qualitative medical aid to patients with such a disease. It is of a greater interest in the modern medical society.

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