New possibilities of pharmacotherapy for immune-mediated inflammatory rheumatic diseases: a focus on inhibitors of interleukin-17

Nasonov E.L.[1, 2]

[1]ФГБНУ «Научно-исследовательский институт ревматологии им. В.А. Насоновой», Москва, Россия; [2]ФГБОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Минздрава России, кафедра ревматологии Института профессионального образования, Москва, Россия
[1]115522 Москва, Каширское шоссе, 34А; [2]119991 Москва, ул. Трубецкая, 8, стр. 2

[1]V.A. Nasonova Research Institute of Rheumatology, Moscow, Russia; [2]Department of Rheumatology, Institute of Professional Education, I.M. Sechenov First Moscow State Medical University, Ministry of Health of Russia, Moscow, Russia
[1]34A, Kashirskoe Shosse, Moscow 115522; [2]8, Trubetskaya St., Build. 2, Moscow 119991

Контакты: Евгений Львович Насонов; **nasonov@irramn.ru**

Contact: Evgeny Nasonov; **nasonov@irramn.ru**

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Prof. **Evgeny L. Nasonov**, MD, PD, Academic Director of V.A. Nasonova Research Institute of Rheumatology B.A. Head of Rheumatology Department, Institute of Professional Education, I.M. Sechenov First Moscow State Medical University, И.М. Ministry of Health of Russia, member of the Russian Academy of Sciences

In recent years, more attention has been focused on Th17 cells that synthesize interleukin-17 (IL-17) in contrast to Th1 and Th2 cells, the marker cytokines of which are interferon-r (IFN-r) and IL-4, respectively. It is precisely these pathological activation and expansion of Th17 cells that are supposed to play a key role in the development of a wide spectrum of immune-mediated inflammatory rheumatic diseases (IMIDs), including rheumatoid arthritis (RA), psoriasis, ankylosing spondylitis (AS), psoriatic arthritis (PsA), inflammatory bowel disease, and systemic lupus erythematosus, which were previously considered as Th1-dependent diseases associated primarily with the hyperproduction of IL-2 and IFN-r. This has served as a powerful stimulus to design new biological agents, the mechanism of action of which is based on blocking the pathological effects of IL-17, others associated with the activation of Th17 cells of cytokines, or small molecules interfering with transcription factors that regulate the synthesis of these cytokines. This review discusses current studies of the mechanisms regulating the formation and functional activity of IL-17 family cytokines, as well as evidence of the importance of these cytokines in the pathogenesis of IIDs. Special attention is paid to the clinical efficacy and safety of anti-IL-17A monoclonal antibody secukinumab used to treat psoriasis, PsA, AS, and RA.
Key words: IL-17/IL-23 axis; interleukin 17; psoriasis; psoriatic arthritis; ankylosing spondylitis; rheumatoid arthritis.
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НОВЫЕ ВОЗМОЖНОСТИ ФАРМАКОТЕРАПИИ ИММУНОВОСПАЛИТЕЛЬНЫХ РЕВМАТИЧЕСКИХ ЗАБОЛЕВАНИЙ: ФОКУС НА ИНГИБИТОРЫ ИНТЕРЛЕЙКИНА 17

Насонов Е.Л.[1, 2]

В последние годы большее внимание привлечено к Th17-клеткам, синтезирующим интерлейкин 17 (ИЛ17), в отличие от Th1- и Th2-клеток, «маркерными» цитокинами которых являются соответственно интерферон γ (ИФНγ) и ИЛ4. Полагают, что именно патологическая активация и экспансия Th17-клеток играют ведущую роль в развитии широкого спектра иммуновоспалительных заболеваний (ИВЗ) человека, включая ревматоидный артрит (РА), псориаз, анкилозирующий спондилит (АС), псориатический артрит (ПсА), воспалительные заболевания кишечника, системную красную волчанку, которые ранее рассматривались как Th1-зависимые заболевания, связанные в первую очередь с гиперпродукцией ИЛ2 и ИФНγ. Это послужило мощным стимулом для разработки новых генно-инженерных биологических препаратов, механизм действия которых основан на блокировании патологических эффектов ИЛ17, других связанных с активацией Th17-клеток цитокинов, или «малых молекул», интерферирующих с факторами транскрипции, регулирующими синтез этих цитокинов. В обзоре обсуждаются современные исследования, касающиеся механизмов регуляции образования и функциональной активности цитокинов семейства ИЛ17, и доказательства значения этих цитокинов в патогенезе ИВЗ. Особое внимание уделяется клинической эффективности и безопасности моноклональных антител к ИЛ17А – препарату секукинумаб при псориазе, ПсА, АС и РА.
Ключевые слова: ось ИЛ-17/ИЛ-23; интерлейкин 17; псориаз; псориатический артрит; анкилозирующий спондилит; ревматоидный артрит.
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According to modern concepts, the central stage in regulation of acquired immunity, which plays a fundamental role in protecting the body from potentially pathogenic factors of ambient (and internal) environment, is occupied by differentiation of naive CD4+ T-cells into T-helper (Th) cells, which synthesize a wide range of cytokines that coordinate the immune response. About 20 years ago T.R. Mosmann and R.L. Coffman [1] formulated an extremely seminal concept of existence of two major subpopulations of these cells - Th1 and Th2: the former induce cell-mediated response against intracellular infections (viruses, bacteria) and participate in the development of chronic (autoimmune) inflammation, while the latter act against extracellular infectious agents (bacteria, parasites, including helminths), toxins and participate in the development of allergic diseases. Later on other subpopulations of CD4+ T-cells were identified; each of them occupies their own place in the variety of physiological mechanisms of immune defence or pathogenesis of human immune-mediated inflammatory diseases (IMIDs), malignant neoplasms and other pathological conditions (Fig. 1).

The biggest attention is focused on Th17 cells that synthesize interleukin (IL)-17 in contrast to Th1 and Th2 cells, the marker cytokines of which are interferon-γ (IFN-γ) and IL-4, respectively [2]. It is precisely these Th17 cells' pathological activation and expansion that are supposed to play a key role in the development of a wide range of human IMIDs, including rheumatoid arthritis (RA), psoriasis, ankylosing spondylitis (AS), psoriatic arthritis (PsA), inflammatory bowel diseases (IBDs), and systemic lupus erythematosus (SLE), which were previously considered Th1-dependent diseases [3]. Moreover, in recent years there have been discussions of Th17 cells participation in carcinogenesis, atopy, atherogenesis, transplantation immunity, obesity [3]. This has served as a powerful stimulus to design new biological agents, the mechanism of action of which is based on blocking the pathological effects of IL-17, or "small molecules" interfering with transcription factors that regulate the synthesis of these cytokines [3].

IL-17, previously identified as cytotoxic T lymphocyte-associated antigen 8 [4], was discovered in 1995 [5]. There are six ligands in the IL-17 cytokine family, including: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F (Table 1) [6]. IL-17A is a dimeric glycoprotein (molecular weight 15 kDa), which consists of 155 amino acids. It is the main representative of structurally related IL-17-cytokines, primarily IL-17F, which has a 50% homology with IL-17A. Homology with other members of the IL-17 family varies from 20% to 50%, which determines both the similarity and differences in their biological effects. IL-17A circulates in the blood stream as a homodimer consisting of two chains of IL-17A or as a IL-17A/IL-17F heterodimer. IL-17A, which is a "marker" cytokine of the IL-17 family, has the strongest "pro-inflammatory" activity. Along with IL-17A, IL-17B, IL-17C and IL-17D are also classified as "pro-inflammatory" cytokines, although their role in the development of inflammation is understudied. IL-17E (also known as IL-25) has the weakest homology with IL-17A and is involved in Th2 cells generation.

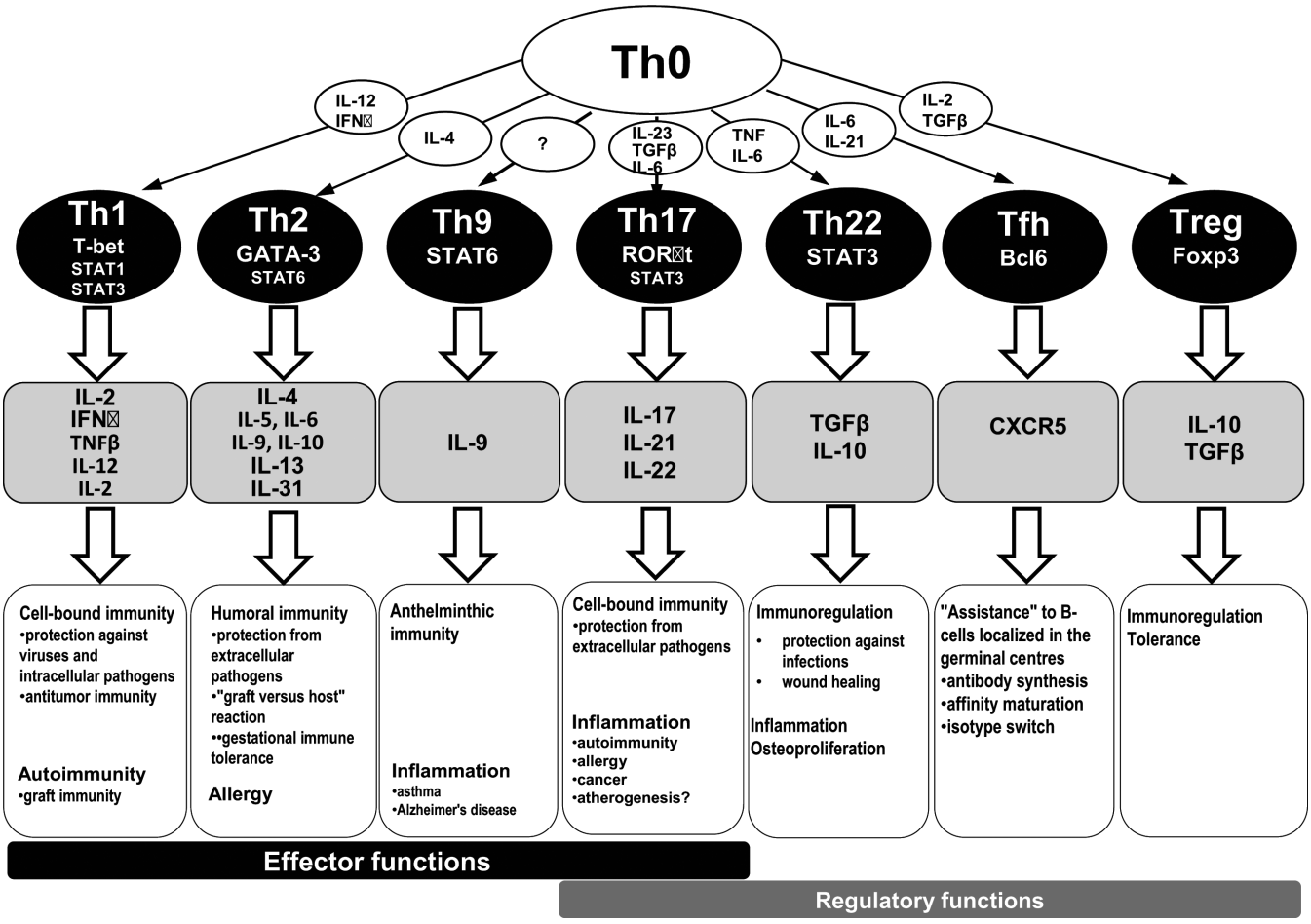

Fig. 1. Main subpopulations of CD4 + T-helper lymphocytes

Table 1 Functional characteristics of IL-17 cytokines

Cytokines	Synonyms	Basic IL-17 synthesizing cells	Main IL-17 effector functions
IL-17A/ IL-17F	CTLA8	Th17, γδ T cells, RORγt + ILC, mast cells, macrophages, neutrophils, keratinocytes, iNKT, etc.	Synthesis of IL-1β, IL-6, IL-8, IL-11, CXCL1, G-CSF, GM-CSF, antimicrobial peptides, activation of NF-κB, MAPK signalling pathways, neutrophils
IL-17B	IL-20, NIRF		
IL-17C	CX2	Epithelial cells	Synthesis of antimicrobial peptides
IL-17D	IL-27		
IL-17E	IL-25	Th17, eosinophils, basophils	Synthesis of IL-4, IL-5, IL-13, IgE, eotoxin, eosinophilia, basophilia

Note. NIRF – neuronal interleukin 17-related factor; iNKT – invariant natural killer T; ILC – innate lymphoid cells; CXCL1 – chemokine (C-X-C motif) ligand 1; G-CSF – granulocyte colony-stimulating factor; GM-CSF – granulocyte-macrophage colony-stimulating factor; NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK – mitogen-activated protein kinase.

The family of IL-17 receptors (IL-17R) was first identified in 1995 and is considered to be a unique type of receptors that differ in structure from other cytokine receptors (Fig. 2) [7]. It includes 5 subunits, IL-17RA → IL-17RE, which have a common transmembrane domain. At the same time, IL-17A, IL-17F and IL-17A/F with various affinity bind to the same receptor complex, consisting of IL-17RA and IL-17RC subunits. IL-17RA is a subunit of IL-25R, including IL-17RA and IL-17RB. There is a theory that IL-17RA blockade can potentially suppress the "anti-inflammatory" effect mediated by IL-17E (IL-25) [8], which may have a negative effect on the efficacy of monoclonal antibodies (MoAbs) to IL-17 receptors. Binding of IL-17 to the corresponding receptor results in the "assembly" of adapter proteins (ACT, TRAF) regulating the activation of important signalling pathways, including NF-κB, C/EBP (CCAT/enhancer-binding proteins), AP1 (activation protein-1) and other transcription factors, regulating "pro-inflammatory" cytokines gene function [6, 7].

The differentiation and proliferation of Th17 cells, first cloned from the synovial tissue of RA patients in 1999 [9], has several stages (initiation, amplification and stabilization), and is regulated by various cytokines and growth factors (Fig. 3, Table

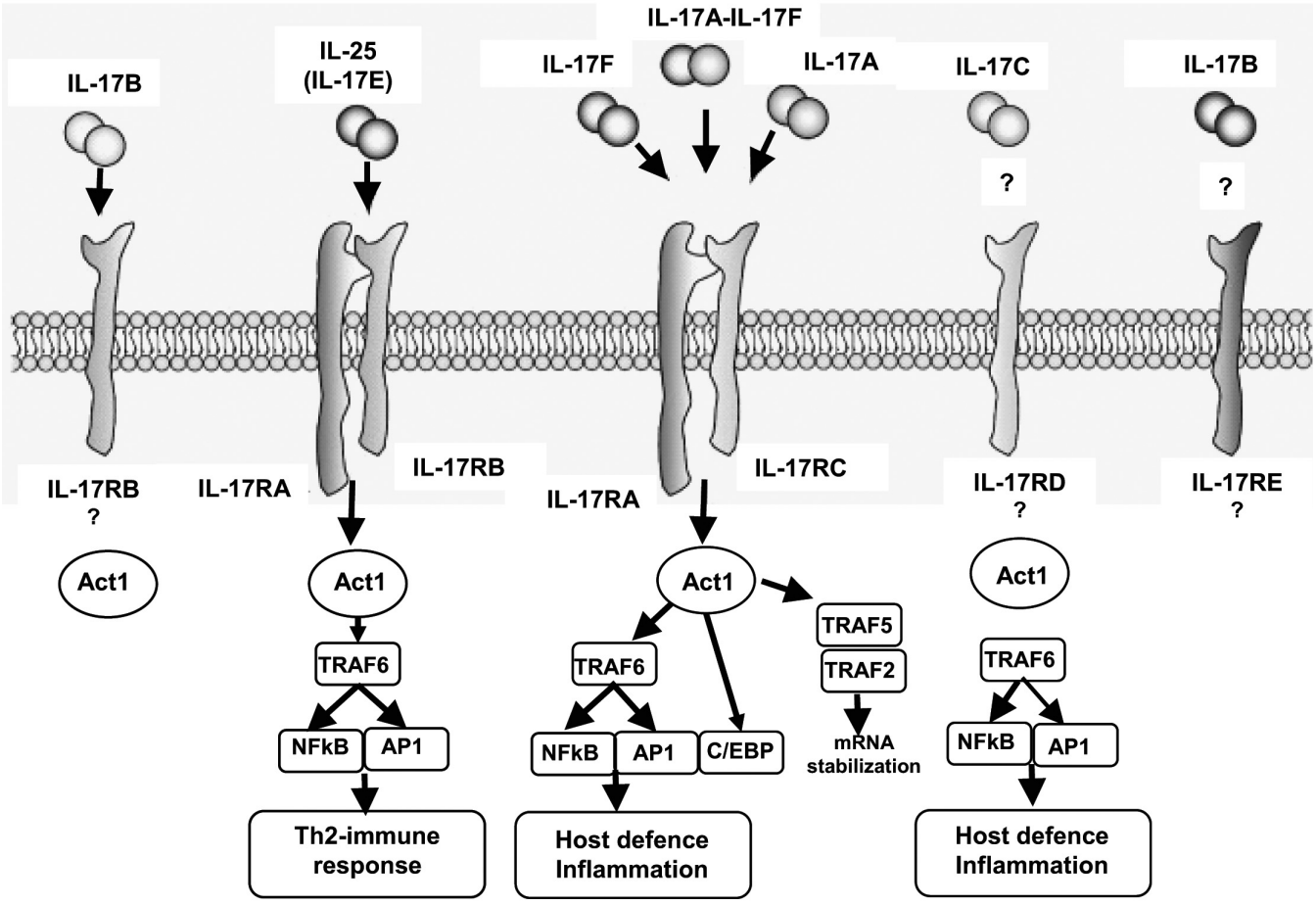

Fig. 2. Characteristics of IL-17 receptors and signalling. ACT1 - NF-κB activator; AP1 – activator protein 1; TRAF – TNF receptor-associated factor; C/EBP – CCAAT-enhancer-binding protein

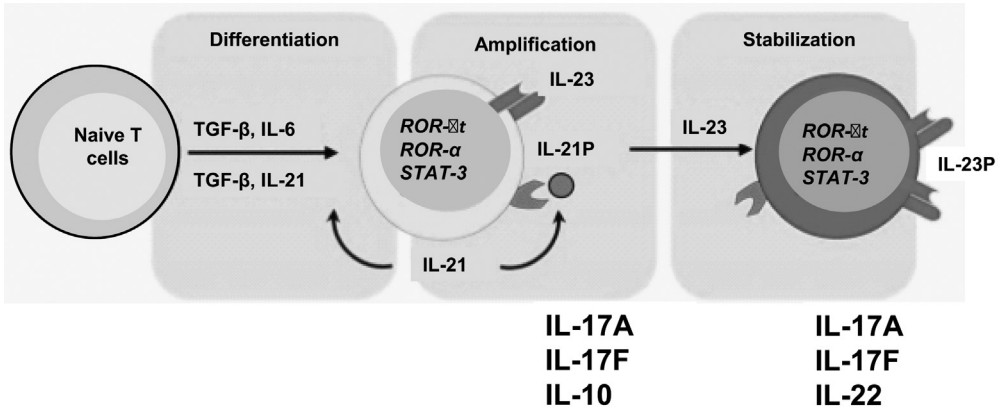

Fig. 3. The stages of "pathogenic" Th17 cells formation. Na?ve T cells activation in the presence of TGFβ initiates Th17 cells differentiation. Th17 cells begin to synthesize IL-21, which "amplifies" the formation of Th17 cells along the "autocrine" pathway. IL-21 induces the expression of IL-23 receptors on differentiating Th17 cells, making them "sensitive" to IL-23 signalling. IL-23 stabilizes the Th17 phenotype, which begins to synthesize IL-17A, IL-17F, IL-22, thereby ensuring that Th17-cells perform effector functions

2). In contrast to IL-12, which has been identified as a key cytokine that induces IFN synthesis, which is characteristic of the Th1 type immune response, the activation of the Th17 immune response is associated with another cytokine, IL-23 [10]. IL-23 and IL-12 are members of the IL-12 cytokine family and have a heterodimeric structure and carry a common subunit (p40). IL-23 comprises p40- and p19-subunits and acts via IL-12Pβ1 and IL-23P, while IL-12 comprises p40 and p35. Although IL-12 and IL-23 are structurally alike, they have different functional activity, regulating the polarization of the immune response in the Th1 and Th17 types, respectively [11]. The leading stage in the functioning of Th17 cells is the binding of IL-23 to the corresponding receptor, which forms the basis of the so-called IL-23/IL-17 axis, the activation of which determines the pathogenic potential of Th17 cells [12]. In the presence of IL-21 and IL-6, and also probably the transforming growth factor β (TGFβ), which initiate Th0-differentiation into Th17 cells and IL-23P expression, IL-23 induces the activation of the main transcription factor of Th17 cells - RORt (retinoic acid-receptor-related orphan receptor) or RORC in humans. Other transcription factors more or less related to the activation of the IL-23/IL-17 axis, include STAT3 (signal transducer and activator of transcription 3) - Jak2/tyk2, IRF4 (interferon regulatory factor 4), AHR (aryl hydrocarbon receptor), BATF (Basic leucine zipper transcription factor ATF-like), Runx1 (runt-related transcription factor 1), and others [12]. It is noteworthy that RORt not only controls the expression of Th17-specific genes but also suppresses the expression of a number of proteins characteristic of other T-cell subpopulations. A significant role in the regulation of Th17 cells functional activity is attributed to CD4 + T-regulatory cells (Treg), the balance between which underlies the immune homeostasis and tolerance. Treg cells, inhibiting RORt expression, suppress the formation of Th17 cells, but under the influence of "pro-inflammatory" cytokines can be transformed into Th17 cells, which represents the so-termed Th17/Treg plasticity phenomenon [13]. An important cytokine associated with activation of the IL-23/IL-17 axis is IL-22 (a member of the IL-10 cytokine family), which is syn-

Table 2 The main cytokines that regulate the differentiation of Th17 cells and are synthesized by Th17 cells

Differentiation of Th17 cells	Inhibition of Th17 cell differentiation	Functional activity of cytokines synthesized by Th17 cells or regulating their function
IL-23 • Survival and expansion of Th17 cells • Th17-cytokine synthesis induction • Decrease in ability of Th17-cells to dedifferentiation and plasticity	IFNγ	IL-17A • Regulation of local tissue inflammation by coordinating the expression of "pro-inflammatory" and "neutrophilic" cytokines and chemokines IL-17F • Recruitment of neutrophils and immune response to extracellular pathogens
IL-6 • Activation of RORγt and IL-21 expression	IL-2	IL-21 • Enhancing the Th17 proliferation by inducing the IL-23P expression
TGFRβ • The transition of Th0 to Th17 cells (in combination with IL-6 and IL-23)	IL-4	IL-22 • Synthesis of antimicrobial peptides and expression of "pro-inflammatory" cytokines by keratinocytes and other nonhematopoietic cells
IL-1β • Th17 differentiation • Increased expression of ROR?t and IRF4 • Maintaining the synthesis of Th17-cytokines after the polarization of the immune response	IL-27	IL-26 • Enhancement of Th17 "pro-inflammatory" response by epithelial cells GM-CSF • Enhancement of the Th17 cells pro-inflammatory function • Differentiation of M1 (inflammatory) macrophages MIP3α • CCR6 ligand TNF-α • Pleiotropic activator and immunity regulator, activating Th17 cells and acting synergistically with IL-17

Note. CCR6 – C chemokine receptor type 6; CD196; IRF4 – interferon regulatory factor 4.

thesized by a special population of T cells - Th22 cells, and Th17 cells and other cells involved in the innate immunity [14]. On the one hand, IL-22 exhibits synergistic effects with IL-17 and TNF-α regarding the development of inflammation, while on the other hand it plays an important role in protecting tissues from damage (including with infectious agents) and in healing and regeneration processes. It is noteworthy that IL-22 prevents the formation of Foxp3 + Treg and induces the resistance of effector T cells to Treg mediated immunosuppression.

It should be especially emphasized that, along with Th17 cells, IL-17 is synthesized by many cellular populations that are localized in various tissues (lungs, intestinal mucosa, skin, etc.) and participate in the regulation of not acquired, but innate immunity. These include CD8 + T cells, RORt T cells, invariant natural killer cells (T-iNKT), mucosal-associated invariant T-cells (T-MAIT), helper T cells and natural killer cells (NKT cells), killer cell immunoglobulin like receptor (KID3DL2), natural Th17 cells, lymphoid tissue inducer cells (LTi), group 3 innate lymphoid cells (ILC3), as well as macrophages, neutrophils and mast cells [15].

IL-17 has a variety of effects (pleiotropic) on different cell populations, which determines the fundamental physiological (protection against infections) and pathophysiological (chronic immune inflammation) role of this cytokine. The basic physiological function of Th17 cells and IL-17 is the immune defence of the body from extracellular bacterial and fungal infections that penetrate the human body through epithelial and mucous barriers [16]. An example of IL-17's important role in anti-infectious immunity is hyper-IgE syndrome (associated with the genetic mutation of STAT3 gene), in which an increase in the sensitivity to Staphylococcus aureus and Candida albicans infection is closely related to the Th17 defect. The development of chronic mucocutaneous candidiasis (an infectious skin disease most often caused by C. albicans) is due to a genetic defect of IL-17RA, IL-17F, Act1, IL-17RS and RORC and autoantibody response to IL-17A, IL-17F and IL-22, which blocks their protective function.

IL-17A (and also IL-17F), binding to IL-17R, expressed on cells involved in the development of inflammation (vascular endothelium, macrophages, fibroblasts, osteoblasts and chondrocytes, etc.) [17], induces the production of "pro-inflammatory" cytokines and chemokines (Table 3). It should be emphasized, however, that IL-17 itself has a relatively weak activity, but exhibits a powerful synergistic effect with other cytokines (TNF-α, IL-1β, IL-22, IFNγ, GM-CSF) with respect to both induction of other "pro-inflammatory" cytokine synthesis and effects of chronic inflammation in general. The synergy between IL-17 and TNF-α is of particular importance. There is evidence that IL-17 stabilizes the TNF-α mRNA, thereby enhancing its synthesis, and induces the expression of type II TNF-α receptors on various cells that participate in TNF-dependent inflammation [3].

The role of the IL-23/IL-17 axis in the development of IMIDs

As already noted, convincing data have now been obtained on the important role of Th17-immune response in the pathogenesis of a wide range of human IMIDs [3, 17-19].

Psoriasis

Psoriasis is the most frequent human IMID, characterized by a high incidence of comorbid diseases, including cardiovascular pathology and diabetes mellitus, metabolic syndrome, depression, and possibly PsA, as part of the so-called psoriatic disease [20, 21]. Characteristic features of psoriasis are the proliferation of keratinocytes and the accumulation in the affected skin of immune cells (T cells, macrophages, leukocytes) and myeloid (CD11 +) dendritic cells (DC) that are involved in the polarization of the immune response both in Th17 and Th1 types [22-24]. These cells produce a wide range of cytokines that, affecting keratinocytes and other skin resident cells, induce hyperproliferation of the epidermis, neoangiogenesis and inflammation of the skin in general. A unique place in the immunopathogenesis of psoriasis is occupied by cathelicidin (cathelicidin/LL-37) and ADAMTS-like protein 5 [25, 26], whose presentation of DCs induces the IL-23 synthesis. In the skin of psoriatic patients an increase in the content of Th17 cells, γδT cells, IL-C3 cells, NK cells, mast cells synthesizing IL-17,

Table 3 Cytokines and other IL-17 induced mediators

	Mediators	Cells
Cytokines	IL-6	Chondrocytes, keratinocytes, fibroblasts, synoviocytes, macrophages, endothelial cells, myofibroblasts, astrocytes
	TNF-α	Macrophages
	IL-1β	Macrophages, chondrocytes, astrocytes, synoviocytes
	IL-10	Macrophages
	IL-12	Macrophages
	GM-CSF	Fibroblasts, synoviocytes
Chemokines	IL-8 (CXCL8)	Keratinocytes, fibroblasts, synoviocytes, epithelial cells, endothelial cells, panacinous myofibroblasts of the large intestine and pancreas
	GROα (CXCL1)	Synoviocytes, epithelial cells, chondrocytes
	CINC	Interstitial epithelial cells
	MIP2 (CXCL2)	Synoviocytes, epithelial cells
	CXCL5	Chondrocytes
	RANTES (CCL5)	Endothelial cells
	MIP3 (CCL20)	Synoviocytes
Other	Complement 3	Skin fibroblasts, subepithelial myofibroblasts of the large intestine
	Factor B	Skin fibroblasts
	TLR 2,4,9	Synoviocytes
	ICAM-1	Skin fibroblasts, keratinocytes
	NO	Chondrocytes, epithelial cells
	PGE2	Macrophages, chondrocytes, synoviocytes

IL-23, IL-22, IL-23R, and TNF-α has been observed [27]. The integral and individual effect of IL-17, IL-22 and TNF-α on keratinocytes leads to the induction of gene transcription, encoding the synthesis of antimicrobial proteins (S100A7) and peptides (LL-37 cathelicidin), as well as "pro-inflammatory" mediators: chemokine ligand 20 (CCL20), CXCL1, 2,3,8, IL-19, IL-20, IL-15, IL-36. The development of epidermal hyperplasia and vascular proliferation are caused by the action of both cytokines (IL-22, IL-19, IL-36) and "classical" growth factors, such as epidermal growth factor, TGF, fibroblast growth factor, endothelial growth factor and platelet-derived growth factor. It is noteworthy that, according to genetic studies, the carriage of a specific single-chain polymorphism of IL-23R and IL-22B genes is associated with a "sensitivity" to the development of psoriasis, which brings psoriasis closer to other diseases associated with the IL-23/IL-17 axis activation.

Spondyloarthritis and psoriatic arthritis

Spondyloarthritis (SpA) is a heterogeneous group of diseases including AS, PsA, reactive arthritis and arthritis associated with IBD [28]. It is noteworthy that according to the modern "rheumatological" classification of PsA, which develops in at least one third of patients suffering from psoriasis, falls into the SpA group of diseases, but despite the development of spondylitis, enthesitis and dactylitis, characteristic of SpA, phenotypically differs from SpA. It is believed that psoriasis without joint damage and PsA should be considered as options for the development of "psoriatic disease", the differences between which are determined by the "profile" of cytokine synthesis and genetic factors [21]. In any case, along with psoriasis, AS and PsA are classic examples of diseases whose development is associated with the activation of the IL-23/IL-17 axis [29-33].

As in psoriasis, there is a correlation between the development of PsA and the carriage of single-nucleotide (protective) polymorphism of IL-23R and IL-23 encoding genes, as well as the polymorphism of the ACT1 gene (TRAF3IP2) involved in IL-17R mediated signalling [34, 35]. An increase in the expression of IL-12p19 – IL-23R, IL-17A – IL-17R was noted in the affected skin and synovial membrane of PsA patients. In vitro experiments have shown that IL-17 induces the hyperproduction of IL-6, IL-8 and matrix metalloproteinase 3 (MMP3) by synoviocytes isolated from the joints of PsA patients. There was an increase in the number of IL-17 + cells and CD22 + CD4 + cells in the peripheral blood of psoriasis and PsA patients. There are data on the correlation between the content of another subpopulation of IL-17 cells – CD8 + in synovial tissue, the activity of inflammation and the severity of joint destruction. In the synovial fluid of PsA patients an increase in the content of Th17 cells and the concentration of IL-17, IL-17R, IL-23, correlating with the severity of arthritis, was noted.

AS is the main representative of the SpA group, the cardinal feature of which is damage to axial skeleton, associated with the development of inflammation in the area of ligaments insertion to the spine and sacroiliac joints (enthesis) [28]. Unlike RA and PsA, which are characterized by bone tissue destruction, a unique feature of AS is the formation of new bone tissue [33]. In addition to the well-proven role of HLA-B27 in AS, recent studies have demonstrated the relation between the polymorphism of the IL-23P coding gene and the propensity to develop AS [34, 35]. Large-scale genome screening has enabled to establish that the carriage of the IL-23P rs11209026 (arg381Gln) variant prevents the development of AS and is associated with a decrease in STAT3 phosphorylation and IL-17 synthesis. It is suggested, that other genes associated with the IL-23/IL-17 axis are also involved in the development of AS (as well as psoriasis and IBD), including IL-6R, IL-12B, IL-27, CADR9 (nuclear transcription factor Y subunit B-4-like), STAT3 and TYK2, as well as epigenetic "autographs" of these genes [35, 36]. According to experimental data, the inflammation associated with the activation of the IL-17/IL-23 axis leads to the development of arthritis, enthesitis [37-39] and new bone tissue in AS. An increase in the concentration of a wide range of "pro-inflammatory" cytokines, including IL-17A, IL-6, TGFβ [40-42], IL-23 [41-44] in the sera of AS patients and the content of various Th17 and Th22 subpopulations in the peripheral blood of SpA patients [45-49]. It has also been established that an increase in the number of KIR3DL2 + Th17 cells interacting with the HLA-B27 homodimer is observed in the blood and synovial tissue of AS patients [50], which contributes to the "survival" and enhancement of IL-17 synthesis by these cells. The recent studies have shown that there is an increase in the number of Th17 memory cells expressing the T-cell receptor (TCR) αβ + CCD161, in the peripheral blood of early (non-axial) SpA patients [51]. It is noteworthy that an increase in the concentration of IL-17A and the number of Th17 cells is observed predominantly in men, but not in women with SpA [52] and does not depend on the concentration of sex hormones. This indicates certain differences in the SpA pathogenic mechanisms in women and in men and allows explaining the nature of a more severe lesion of the axial skeleton in the latter, despite similar pain and functional status [53]. It should be noted that not only Th17 cells but also cells of the innate immune system actively synthesize IL-17 especially in the affected tissues of SpA patients [54-57]. In particular, it has been shown that ILC3 cells when stimulating IL-23 synthesize an excessive amount of IL-17, IL-22 and other "pro-inflammatory" cytokines [57].

Another important aspect of this problem is related to the role of intestinal inflammation in SpA pathogenic mechanism [58–60]. According to experimental data, "transgenic" mice carrying the HLA-B27 and β2-microglobulin genes observed the development of intestinal inflammation that correlates with an increase in the IL-12 and IL-17 expression in the inflamed tissue [61, 62]. A violation of the intestinal microbiota in transgenic HLA-B27 rats was discovered in comparison with wild rats [63]. Pathological changes in the intestinal microflora (dysbiosis) have been revealed in patients suffering from AS, PsA, and IBD, and are associated with differentiation of cells synthesizing IL-17 and IL-22 [64, 65]. In recent studies, it has been shown that in AS patients an increase in IL-23 expression and an abnormal content of DC, T- and IL-C3 cells that synthesize IL-17 and IL-22 in the intestinal mucosa are observed [66, 67]. In the terminal section of the small intestine, an increase in the expression of IL-23p19 mRNA was observed in patients with SpA and Crohn's disease. In this case, monocytes infiltrating the intestinal wall, synthesize IL-23, and Panet cells synthesize IL-17 and IL-23 [68].

Of special interest is the study of the role of the IL-23 / IL-17 axis activation in the development of enthesitis, a characteristic manifestation of SpA [39, 69, 70]. It is believed that local synthesis of IL-23 is triggered under the influence of mechanical stress and/or dysbiosis in HLA-B27 carriers, including as part of "unfolded protein response" associated with HLA-D27 misfolding. This, in turn, leads to the activation of resident T cells localized in enthesis that begin to synthesize both IL-17 (and TNF-α) that induce the development of inflammation, and IL-22 that causes osteoproliferation.

Rheumatoid arthritis

At present, a large number of studies have convincingly demonstrated the important role of IL-17 in the immunopathogenesis of RA, which are summarized in a series of reviews [18, 71, 72]. In IL-17 deficient mice induction of collagen arthritis is complicated [73], and the administration of IL-17A inhibitors attenuates articular inflammation and radiographic signs of joint destruction in experimental arthritis [74-77]. In patients with RA the concentration of IL-17A in the serum and synovial fluid is significantly higher than in patients with osteoarthritis (OA) and in the controls [78-82], and correlates with the activity and severity of the pathological process, in particular with the hyperproduction of antibodies to cyclic citrullinated peptides (anti-CCP) [78-80]. It is noteworthy that the pathogenic role of Th17 cells is especially evident at the early stage of RA. Thus, the concentration of IL-17 in the sera of patients with early RA (<9 weeks) is significantly higher than in the later stages of the disease [82], and the level of IL-17 in healthy people who subsequently developed RA is higher than in patients after the onset of the disease [83]. Nucleotide polymorphism of CCR6 regulatory variant (specific marker of Th17 cells) correlates with increased expression of CCR6, IL-17 concentration and the risk of RA development [84]. There is evidence that it is in the early phase of RA that the "plasticity" of Th cells is realized, in particular, manifested in the conversion of Th17 cells into Th1 cells, leading to the formation of so-called "non-classic Th1 cells" [85]. It has been shown in recent studies, that an increase in the number of Th17 cells carrying CD161 is noted in patients with early RA, which are considered to be a "marker" for the transformation of Th17 cells from Th1 cells [86]. It is noteworthy that methotrexate (MT), the most effective drug for RA treatment, normalizes the number of Th17 cells, which justifies high MT efficacy in the early stage of RA [87]. It has been shown in recent studies, that in the course of the treatment with TNF- inhibitors, those responding to therapy have a significant decrease in the concentration of IL-17A and circulating Th17 cells in the peripheral blood. In contrast, in patients resistant to TNF- inhibitors, an increase in the level of Th17 and IL-17A concentration was noted, despite a decrease in the level of TNF-. At the same time, the high basal level of IL-17 was the only independent predictor of resistance to treatment with TNF- inhibitors [88]. Resistance to TNF- inhibitors is associated with an increase in the number of Th17 cells in the peripheral blood, p40 (IL-12 and IL-23 subunit) concentrations, and a tendency for more pronounced production of IL-17 ex vivo by peripheral mononuclear cells isolated from the blood of RA patients. In addition, the high basal level of Th17 cells is associated with a lack of positive dynamics of DAS28 index on the background of therapy [89].

In general, the study of the distribution of the Th17-cell subpopulations and Th17-cytokines in SpA and RA indicates, on the one hand, the significance of activation of the IL-17/IL-23 axis in the immunopathogenesis of both diseases; and the existence of various mechanisms for the regulation of the "pathological" Th17-immune response in these diseases on the other hand. We will note only some facts, the true pathophysiological and clinical significance of which requires further study. For example, there was a correlation between IL-22 expression and the frequency of detection of Th17 cells in AS, but not in RA patients [47]. At the same time, the number of Th22 and Th17 cells correlates with the activity of inflammation in RA, but not with SpA. Although IL-23 (and also CCL20) is expressed in the synovial membrane of the joints in both diseases, the IL-23 serum level is only associated with disease activity in RA [48]. The severity of synovial cell hyperplasia correlates with the level of IL-17, IL-23 and CCL20 in RA, but not in SpA. Synovial tissue of SpA patients (unlike in RA patients) contain mast cells (c-Kit +) that actively synthesize IL-17. In case of SpA there was an increase in the number of γδ T cells expressing IL-23P, an increase in which in the peripheral blood is associated with hyperproduction of IL-17. In general, all these data indicate a more pronounced activation of the innate Th17 immune response in SpA than in RA, and the prevalence of the autoinflammatory component in the immunopathogenesis of the disease, in contrast to the acquired Th17 and Th1 types of immune response underlying the autoimmune pathological process, observed in RA patients [90]. Comparative analysis of gene expression (Affymetrix array) in the skin and synovial membrane in PsA patients has shown that the "genetic profile" of changes in the synovial membrane is more reminiscent of pathological changes in the skin than in joints with other types of arthritis [91]. At the same time, according to the immunomorphological study of the material obtained from joint biopsy in patients with RA, PsA and OA, marked heterogeneity of IL-17A, IL-17F and their receptors expression in the synovial tissue was noted [92]. This makes it possible to partially explain the results of clinical studies, which indicate significant differences in the effectiveness of therapy with IL-17 inhibitors in these diseases.

Behcet's disease

Behcet's disease (BD) is a systemic vasculitis of unknown etiology, characterized by recurrences of ulcerative process in the oral cavity and genitals, eye lesions, joint damage, gastrointestinal tract, central nervous system and other organs failure [93]. In the serum of BD patients, IL-17 concentration correlating with the activity of the disease was noted [94-96], and an increase of IL-23 mRNA content in leukocytes, IL-23 in serum and IL-17 synthesis in supernatants of cultured leukocytes [96]. Certain polymorphisms of IL-23R–IL-12RB2 associated with the risk of BD development have been identified in a large-scale genetic studies [97, 98].

Systemic lupus erythematosus

SLE is a chronic autoimmune disease of unknown etiology, characterized by a systemic immune-inflammatory lesion of vital organs and an extraordinary variety of clinical manifestations [99]. A characteristic feature of SLE is pronounced activation of humoral and cellular immunity, the most vivid manifestation of which is the synthesis of autoantibodies to a wide spectrum of core antigens. In recent studies, data have been obtained that indicate the potential pathogenic significance of the Th17-type immune response in this disease. Thus, according to experimental studies MRL and B6 mice with a spontaneously developing lupus-like disease demonstrate an increased IL-17 concentration in serum [100, 101]. It is not possible to induce the development of lupus nephritis in the mice deficient in the IL-17 synthesis [102, 103]. An increase in the concentration of IL-17 [104-107], IL-6, IL-23 [107] in the sera of SLE patients and the level of circulating Th17 cells [107] correlates with the clinical activity of the disease and the severity of kidney damage from biopsy data [107]. Infiltration with Th17 cells was observed in renal biopsy specimens from patients with lupus nephritis [108, 109], and IL-17 concentration in renal tissue correlates with the severity of microhematuria, proteinuria, serum urea level, and clinical activity of SLE [110]. Along with IL-17 there is an increase in the concentration of IL-23 in the sera of patients

with SLE [111, 112]. It was found that overexpression of IL-23 is driven by an increase in the binding of the IFN-regulatory factor 3 and the promoter site of IL-23p19 [113]. It was also noted that in SLE patients the expansion of IL23R + cells including subpopulations of both CD4 + and CD8 + lymphocytes is observed, and an increase in the levels of IL-23 + and IL-17 + cells correlates with the SLE activity [114]. It is believed that an increase in the concentration of IL-23, IL-22, as well as the content of T cells synthesizing IL-22, can determine the heterogeneity of SLE as a clinical syndrome. For example, a high level of IL-23 (and IL-22-synthesizing T cells) is associated with skin lesion and serositis to a greater extent than with kidney damage [115, 116], and a high level of IL-17 is associated with CNS damage rather than with the overall activity of SLE. It is noteworthy that in IL-17 deficient mice there is no synthesis of anti-ssDNA, anti-RNP and antichromatin antibodies, but the synthesis of anti-dsDNA is preserved.

Sjogren's Syndrome

Sjogren's syndrome (SS) is a systemic autoimmune disease characterized by autoimmune damage to the salivary and lacrimal glands, as well as by systemic manifestations that affect the skin, lungs, kidneys, and nervous system [117]. In recent years, numerous data have been obtained, indicating the important role of Th17 cells in the immunopathogenesis of this disease [118-121]. In the inflamed tissue of the salivary glands of patients with SS, massive infiltration with Th17 cells is observed [122, 123], which along with IL-17 synthesize IL-21, IL-22, IL-23 and IL-6 [124, 125]. An increase in the concentration of IL-22 in the sera of SS patients correlates with the severity of xerostomia, an increase in the concentration of rheumatoid factor (RF), anti-SSB antibodies and hypergammaglobulinemia [126]. In the peripheral blood of patients with SS, an increase in the Th17 cell subpopulation (CD4 + CD161 +) associated with activity (ESSDAI index ⩾4), laboratory parameters (ESR, hypergammaglobulinemia, thrombocytopenia, anti-SSB) and severity of disease has been observed [127].

Pharmacotherapy of IL-17-associated IMIDs: focus on secukinumab

The therapeutic efficacy of Th17 cell inhibition and IL-17 synthesis in human IMIDs has been first demonstrated in patients with psoriasis treated with ustekinumab, which is a MoAb to IL-12/IL-23 [128]. However, since these antibodies inhibit not only Th17 but also the Th1 type of immune response, the clinical value of inhibition of Th17 activation alone has not been proven. This served as the basis for the development of therapeutic approaches related to direct inhibition of the effects of IL-17 in human IMIDs [129]

Secukinumab (SEC, Secukinumab, Novartis) is a fully human IgG1 MoAb that binds to human IL-17A with a high affinity and neutralizes the activity of this cytokine. This medicinal product is intended for subcutaneous (s.c.) administration, although the effectiveness of intravenous (i.v.) infusion is the subject of special studies [130].

A study of pharmacokinetic parameters was performed in patients with psoriasis and PsA: after the administration of SEC, the serum level of IL-17A (free and associated with SEC) reaches the plateau, and then slowly decreases, which reflects the kinetics of MoAbs to IL-17A clearance associated with IL-17A. The dynamics of concentration of IL-17F was not observed, which indicates the selectivity of SEC in respect of IL-17A. Based on the study of the pharmacokinetic parameters of SEC in patients with psoriasis, it was found that after the administration of a saturating dose (once a week for a month) the maximum SEC concentration in serum is reached within 31-34 days. The peak concentration in the equilibrium state (Cmax ss) after the s.c. administration of 300 mg and 150 mg of the drug after 20 weeks is 55.2 μg/ml and 27.6 μg/ml, respectively. After a single intravenous injection, the absolute bioavailability of the SEC is 73%, and the volume of distribution is 7.10 – 8.60 l, which indicates a limited marginal distribution of the agent. The duration of half-life of SEC in patients with psoriasis is 27 days. In PsA patients, the bioavailability of SEC is 85%, the clearance of the drug is independent of age and increases with increasing body weight. Data concerning the interaction of SEC with the CYP450 enzyme have not been obtained. There were no adverse interactions with the administration of SEC together with MT and glucocorticoids.

Materials relating to the main studies of SEC administration to patients with psoriasis, PsA and AS are summarized in Table 4.

Psoriasis

Phase II randomized placebo-controlled study (RCT) investigated the efficacy of SEC in 125 patients with moderately severe/severe psoriasis. The injection of SEC once every 4 weeks resulted in a significant improvement in the PASI75 (Psoriasis Area and Severity Index) index in 82% of patients receiving 150 mg of SEC ($p<0.001$) and 57% of patients with a 75 mg SEC dose ($p = 0.002$), compared with 9% in the PL group [131]. Later on several large-scale Phase III RCT (ERASURE, FIXTURE, FEATURE) were carried out, which confirmed the very high efficacy of SEC in psoriasis treatment and served as the basis for its official registration for the treatment of this disease [132, 133]. It is noteworthy that according to the data of CLEAR RCT ($n = 676$), SEC was more effective than etanercept (ETN), a TNF-α inhibitor [134]. After 52 weeks, improvement in the PASI 90 index was noted in 76% of the patients receiving SEC and 61% of the patients in the ETN group ($p <0.0001$), the PASI 100 effect was noted in 46% and 36% of patients ($p = 0.0103$), respectively, while the general effect in the opinion of the doctor (pure or almost pure skin) was registered in 80% and 65% of patients ($p <0.001$).

Psoriatic arthritis

A Phase II RPC evaluated the efficacy of SEC in 42 patients with active PsA. After 6 weeks there were no significant differences in efficacy – achieving 20% improvement – between the patients receiving SEC and PL (39% vs 23%; $p = 0.27$) under the American College of Rheumatology (ACR20, the "primary endpoint") criteria. Nevertheless, the SEC group demonstrated a significant effect on the "secondary end points", namely, the dynamics of acute phase parameters (ESR and C-reactive protein - CRP) and quality of life parameters [135].

The results of FUTURE I and FUTURE II, Phase III RCTs, convincingly demonstrated the efficacy of SEC treatment for PsA patients [136, 137]. The "primary endpoint" in both studies was the ACR20 response. "Secondary end points" included the PASI 75 and PASI 90 responses, the dynamics of the DAS29-CRP index, SF-36, HAQ, dactylitis and entesitis. The main results of FUTURE 1 and FUTURE 2 studies are summarized in Table 4.

The FUTURE I study included 660 patients with PsA randomized by groups receiving i.v. SEC infusion, and then 150 mg or 300 mg of SEC, s.c., and a PL group. The data from long-

Table 4 Major SEC RPCSs on psoriasis and rheumatic diseases

Authors	Study Design	Number of patients	Doses, mode of administration	Primary endpoints	Achievement of the primary endpoint	Outcomes
			Psoriasis			
K.A. Papp et al. [131].	Phase II	125	25 mg, 75 mg, 150 mg, PL s.c. once in 4 weeks	PASI75 after 12 weeks	Yes	150 mg (82%; p <0.001), 75 mg (57%; p <0.002), PL (9%)
R.G. Langley et al. [132].	III (ERASURE)	738	150 mg, 300 mg, PL After iv saturation dose sc once every 4 weeks	PASI75 after 12 weeks	Yes	300 mg (81.6%), 150 mg (71.6%), PL (4.5%) p<0.001
R.G. Langley et al. [132].	III (FIXTURE)	1306	150 mg, 300 mg, PL, ETC	PASI75 after 12 weeks	Yes	300 mg (77.1%), 150 mg (67.0%), ETC (44.0%), PL (4.9%) p<0.001
A. Blauvert et al. [133].	III (FEATURE)	177	150 mg, 300 mg, PL, s.c., once a month	PASI75 after 12 weeks	Yes	300 mg (75.9%), 150 mg (69.5%), PL (0%) p<0.0001
			Psoriatic arthritis			
P.J. Mease et al. [136].	III (FUTURE 1)	606	150 mg, 75 mg, PL After i.v. saturation dose s.c. once every 4 weeks	ACR20 after 24 weeks	Yes	150 mg (50%), 75 mg (50.5%), PL (17.3%) p<0.001
I.B. McInnes et al. [135].	III (FUTURE 2)	397	75 mg, 150 mg, 300 mg, PL After i.v. saturation dose s.c. once every 4 weeks	ACR20 after 24 weeks	Yes	300 mg (54%, p <0.001), 150 mg (51%, p <0.0001), 75 mg (29%; p = 0.39), PL (15%)
ClinicalTrial.gov	III (FUTURE 4)	SEC (150 mg, s.c.) in pre-filled syringes with and without saturating dose; a 2 year long term efficacy, safety and tolerability assessment in patients with active PsA.				
ClinicalTrial.gov	III (FUTURE 5)	SEC (150 mg and 300 mg, s.c.) in pre-filled syringes with and without saturating dose; a 2 year long term efficacy (including slowing radiographic progression), safety and tolerability assessment in patients with active PsA.				
			Ankylosing spondylitis			
D. Baeten et al. [143].	II	30	10 mg/kg, i.v., twice in 3 weeks	ASA20 after 16 weeks	Yes	10 mg/kg (59%), PL (24%)
D. Baeten et al. [144].	III (MEASURE 1)	371	10 mg/kg, i.v., then 75 mg or 150 mg, s.c., i.v. after 2 weeks, s.c. after 4 weeks	ASA20 after 16 weeks	Yes	10 mg/kg, i.v. → 75 mg, s.c. (59.7%) and 10 mg/kg, i.v. → 150 mg, s.c. (60.8%), PL (28.7%) p<0.01
D Baeten et al. [145].	III (MEASURE 2)	219	75 mg, 150 mg, PL	ASA20 after 16 weeks	Yes	150 mg (61.1%, p <0.0001), 75 mg (41.1%; n/a), PL (28.4%)
ClinTrial.gov	III (MEASURE 3)	Long-term maintenance of the SEC efficacy (3 years) in patients who "responded" to the therapy after 16 weeks				
ClinTrial.gov	III (ASTRUM)	Assessment of clinical efficacy and the possibility of reducing the dose of NSAIDs (NSAIDs-saving effect)				
			Rheumatoid arthritis			
M.C. Genovese et al. 151 (152)	II	237	25 mg, 75 mg, 150 mg, 300 mg, PL, s.c., twice a month	ACR20 after 16 weeks	No	25-300 mg (36.9-53.7%), PL (34%)
W. Tlustochowicz et al. [153].	II	221	10 mg/kg, i.v., then 150 mg, s.c., every 4 weeks	ACR20 after 12 weeks	No	SEC - 49.2%, PL - 40.9%

Note. ERASURE – Efficacy of Response and safety of Two fixed secukinumab Regimens in psoriasis; FIXTURE – Full Year Investigative Examination of Secukinumab vs Etanercept using Two Dosing Regimens to Determine Efficacy in Psoriasis; PL – placebo, ETC - etanercept.

term (104 weeks) SEC administration showed a persistent therapeutic effect [138]. At the end of the observation period, the ACR20/50/70 response among the patients treated with 150 mg of SEC was observed in 73.9%/46.4%/28.1%, and among the patients who received 75 mg of SEC it was observed in 68.6%/35.55%/22.5%, respectively. Positive dynamics of skin lesions (PASI 75) was observed in 82.9% (150 mg SEC) and in 70.2% of patients (75 mg SEC); and as per PASI 90 it was observed in 69.5% and 50% of patients, respectively. The ACR20 response among the patients who did not receive TNF-α inhibitors occurred in 80.0% (SEC 150 mg) and 72.9% (SEC 75 mg). Corresponding indices in TNF-α inhibitors resistant patients were 55.3% and 54.8%. The absence of radiographic progression was detected in 84.6% (SEC 150 mg) and 83.9% (SEC 75 mg) of patients.

FUTURE 2 study evaluated the efficacy of different doses of SEC (75 mg, 150 mg and 300 mg initially every week for 4 weeks, followed by another dose every 4 weeks) in 397 patients with PsA [139]. The use of MT at a dose of ⩽25 mg per week was allowed. After 24 weeks, the efficacy of SEC (ACR20) was noted at all doses: SEC at 300 mg demonstrated efficacy in 54% of the patients, SEC at 150 mg - in 51% of the patients, SEC at 75 mg - in 29% of the patients and the PL demonstrated efficacy in 15% of the cases. Significant response has also been achieved with regard to "secondary endpoints", including PASI 75, PASI 90, DAS28-CRP and ACR50, but only when administering SEC at 150 mg and 300 mg. The SEC treatment rates were higher in those patients who had not previously received TNF-α inhibitors. A post-hoc analysis of the FUTURE 2 trial results showed that after 24 weeks the PsA patients who had not previously been treated with TNF-α inhibitors (n = 258), ACR20 response to the therapy was observed in 58.2% (SEC at 300 mg; p < 0.001), 63.5% (SEC at 150 mg; p <0.001), and 45.5% (SEC at 75 mg; p <0.001) of the cases and only in 14.3% of the patients in the PL group [138]. In patients resistant to TNF-α inhibitors (n = 139), the efficacy of SEC was lower: in 45.5% (p <0.001), 29.7% (p <0.001) and 14.3% of patients, respectively. At 52 weeks (post-random-

ization phase) in patients who did not receive TNF-α inhibitors, the ACR20 response occurred in 68.7%, 79.4% and 58.5% of patients who received SEC at doses of 300 mg, 150 mg and 75 mg, respectively; whereas among TNF-α inhibitors resistant patients, the therapeutic response was achieved in 54.5%, 37.8% and 35.3% of the cases, respectively. These data suggest that SEC at a 150 mg dose is most indicated for treatment of patients who have not previously received TNF-α inhibitors, whereas in the case of TNF-α inhibitors resistant patients it is more appropriate to administer high (300 mg) doses of SEC.

Data on the comparative efficacy of SEC (FUTURE 1 and FUTURE 2 studies) and human MoAbs to TNF-α adalimumab (ADA) (ADEPT study) [140] are of interest. Preliminary results indicate a higher efficacy of ADA in relation to lesions of both joints and skin (in comparison with the PL). That way, the ACR20/50/70 response was observed in 43.2%/30.5%/23.9% of the patients treated with ADA (40 mg once every 2 weeks) and in 33.7%/27.5%/17.9% of the patients, who received SEC at the 150 mg dose; with respect to PASI75 and PASI90 responses, the rates were 59.2% and 42.4% (ADA) and 46.1% and 35.7% (SEC at a 150 mg dose), respectively. Similar data were obtained by analyzing the efficacy of SEC at a dose of 300 mg. The NNT (number needed to treat) value regarding the number of ACR20 responders was 2.3 for ADA, 3.0 for SEC 150 mg and 2.7 for SEC 300 mg. With respect to PASI75, the corresponding NNT values were 1.7; 2.2 and 1.9. The data of another meta-analysis did not reveal significant differences in the values of the NNT (ACR20) index when comparing ADA, golimumab (GLM), infliximab (INF), cerolizumab pegol (CZP) and SEC (150 mg and 300 mg), which in all cases was below 3 [141]. CZP, ETN and especially ustekinumab (UST) were less effective: NNT ranged from 3.2 to 6.3. With respect to PASI75, these values for SEC (150 mg and 300 mg) did not differ from those characteristic of ADA, INF and GLM therapy: NNT <2 in all cases. There were no differences in the efficacy of SEC and UST in PsA patients, resistant to TNF-α inhibitors. Finally, according to the results of a meta-analysis carried out by I.B. McInnes et al. [142], in relation to the ACR20/50/70 response, SEC is superior to UST and apremilast (a phosphodiesterase 4 inhibitor) and is not inferior to TNF-α inhibitors; as for PASI50/75/90 response, SEC (300 mg) is significantly more effective than ADA, CZP, ETN, GLM (50 mg) and apremilast.

Ankylosing spondylitis

According to a Phase II RCT, which included 30 patients with moderate-to-severe/severe AS, SEC treatment (three i.v. infusions) in 6 weeks resulted in an improvement in the ASAS20 index in 59.2% of the patients (compared with 24.5% of the PL patients). In the course of the dynamic observation (94 weeks), it turned out that SEC treatment (3 mg/kg every 4 weeks) is associated with regression of inflammatory changes in the spine according to MRI data [143].

Phase III MEASURE 1 (n = 371) and MEASURE 2 (n = 219) data indicate a rapid and significant improvement in AS symptoms during SEC treatment [144]. In MEASURE 1 study, patients were administered SEC 10 mg/kg i.v. at Week 1, in 2 and 4 weeks, and then 150 mg or 75 mg every month. In MEASURE 2 study, SEC was administered as a s.c. injection (150 mg or 75 mg) at Weeks 1, 2, 3, and then (starting with Week 4) every 4 weeks. In MEASURE 1 study, patients in the PL group who did not get ASAS20 response by Week 16 were transferred to the SEC treatment group at Week 16; and those patients in the PL group who got ASAS20 response by Week 16 were transferred to the SEC treatment group at Week 24 at the earliest. In MEASURE 2 study, all patients in the PL group were transferred to the SEC treatment group at Week 16, regardless of the therapeutic response. In both studies, the patients from the PL group, when switched to the SEC therapy, were randomized in groups (1:1) who received either 150 mg or 75 mg of SEC, s.c., every 4 weeks. In both studies, disease-modifying anti-rheumatic drugs and prior therapy with TNF-α inhibitors were tolerated, but the vast majority of patients did not have a history of taking the latter.

According to MEASURE 1 study, at Week 16 the ASAS20 response was noted in 61% of the patients in the SEC 150 mg group; in 41% of the patients in the SEC 75 mg group and in 28% of the patients in the PL group ($p < 0.001$ when comparing SEC150 mg and PL; $p = 0.10$ when comparing SEC 75 mg and PL). A follow-up analysis (in 16 and 24 weeks until Week 102), when all the patients were administered SEC (150 mg or 75 mg), showed the continued efficacy of the therapy. The ACR20 response was registered in 79.3% of the patients who received SEC at 150 mg, and in 72.1% of patients who received SEC at 75 mg, and ACR40 response was registered in 64.4% and 53.5%, respectively. Partial remission (ASAS criteria) occurred in 32.2% and 23.3% of patients, respectively [145].

A follow-up analysis (at Week 52) of the MEASURE 2 study results indicates the efficacy of long-term150-mg SEC treatment for all "primary" and "secondary" endpoints used to evaluate the effectiveness of AS therapy [146]. So, for instance, if at Week 16 the ACR20 response occurred in 61.1% of patients, then at Week 52 – in 62.5%; ACR40 response occurred in 36.1% and 48.6% of patients, respectively. Partial remission under ASAS criteria developed at Week 16 in 13.9% of patients (in the PL group - in 4.1%), and at Week 52 in 22.2% of patients.

In a more detailed analysis of MEASURE 1 [146] and MEASURE 2 studies, it turned out that, depending on the previous therapy, SEC effectively controls AS activity both in patients who did not receive TNF-α inhibitors and in TNF-α inhibitors resistant patients [147, 148]. Thus, in the group of patients who did not receive TNF-α inhibitors, the share of patients getting the ASAS20 response was 68.2%, while in the PL group it was 31.1% ($p < 0.001$), and in the group of TNF-α inhibitors resistant patients it was 50% and 24.1%, respectively ($p < 0.05$). Similar data were obtained from a pool analysis of MEASURE 1 and MEASURE 2 studies [147].

According to the pilot study, based on MRI data, a 94-week SEC treatment leads to a reduction in bone marrow edema in 87% of the AS patients (n = 10) [149]. It should be emphasized that suppression of the inflammation detected during MRI is critical for slowing the radiographic progression of the disease. When analyzing the MEASURE 1 study results, it was found that 80% of the patients undergoing SEC treatment (during 104 weeks) demonstrated no radiographic progression of the spinal lesion (mSASSS ⩽0) compared to the baseline, while "new" syndesmophytes, lacking before the start of the SEC treatment were found only in 5% of the patients. This study confirmed earlier findings that the male gender (the mean mSASSS dynamics was 0.38 ± 2.79 in males and 0.08 ± 1.58 in females), an increase in the concentration of CRP (0.47 ± 2.66 in males and 0.02 ± 2.27 in females) and the initial presence of syndesmophytes (0.47 ± 3.20 and 0.02 ± 0.26) are risk factors for the spine injury advancement [150].

Rheumatoid arthritis

The first study of RA treatment with SEC included 52 patients with high activity, which persisted despite MT treatment [129]. The patients were randomized into several groups: PL and two i.v. infusions of SEC 10 mg/kg with a 3 week interval. The duration of follow-up was 16 weeks. According to the preliminary calculation, significant differences in efficacy between SEC and PL (ACR20 response) were to be achieved at $p<0.20$ value. After 6 weeks, the ACR20 response to therapy was achieved in 27% of the patients in the PL group and in 46% of the patients in the SCC group ($p = 0.12$). The positive response to SEC was rapid. After 4 weeks, the ACR20 response occurred in 50% of the patients receiving SEC and in 31% of the patients in the PL group ($p = 0.013$) and maintained for 16 weeks (54% vs 31%, $p = 0.08$). Initial data were obtained with respect to the dynamics of the DAS28 index ($p = 0.16$) and CRP level ($p = 0.001$). When analyzing the ROC curve, SEC was more effective than PL in terms of ACR20 response ($p = 0.01$), DAS28 index ($p = 0.03$) and CRP dynamics ($p = 0.002$). The overall frequency of adverse reactions (AR) was similar (81% on the back of the SEC therapy and 65% on the back of PL administration). There were no serious ARs. Then, a multicentre RCT (Phase II) was carried out, which included 273 patients with active RA despite receiving a stable dose of MT (7.5–25.0 mg/week) [151]. The patients were randomized into several groups: PL, SEC 25 mg, 75 mg, 150 mg and 300 mg every 4 weeks. Treatment with glucocorticoids was allowed (at a <10 mg/day dose). The "primary endpoint" was the ACR20 response at Week 16 on the back of the drug therapy vs. PL treatment. Although the efficacy of the therapy in the compared groups did not differ statistically, a larger number of patients receiving a high dose of SEC achieved the "primary endpoint" compared with the patients receiving PL. ACR20 response was registered in 34%, 47%, 47% and 54% of the patients receiving SEC at a dose of 25 mg, 75 mg, 150 mg and 300 mg, respectively, and in the PL group is occurred in 36% of the patients. At the same time, according to the DAS28-SRB index dynamics, the SEC therapy (25 mg, 150 mg and 300 mg) was significantly more effective than PL administration, and these differences were noticeable starting from Week 2 of therapy. After Week 16, the concentration of CRP was significantly lower on SEC treatment than in the PL group. It is noteworthy that the efficacy of therapy was associated with a higher basal level of CRP (> 10 mg/l) in patients who received SEC at doses of 150 mg and 300 mg. Patients who had a marked effect of SEC therapy, demonstrated a significant positive change in the Quality of Life indicators (EuroQol, SF-36 and FACIT-FATIGUE indices). In the open phase of this study, those patients who did not "respond" to SEC treatment at doses of 25 mg and 75 mg continued treatment with the drug at a dose of 150 mg; those who did not "respond" to 150 mg were transferred to 300 mg, and those receiving 300 mg continued treatment with SEC at the same dose [152]. The patients from the PL group were administered SEC at a 150 mg dose. The duration of treatment was 52 weeks. The most pronounced effect throughout the study occurred in patients who received SEC at a 150 mg dose. After 24 weeks, the ACR50 response was registered in 50% of the patients, and after 52 weeks - in 55%, which was associated with the positive dynamics of the HAQ index: -0.6 and -0.8, respectively. The frequency of remission development under EULAR criteria in the group of patients who received SEC at a dose of 150 mg was 12% after 16 weeks, 30% after 24 weeks and 40% after 52 weeks. Those patients who did not initially respond to the treatment did not demonstrate a significant clinical effect upon dose escalation.

In another Phase II study, the efficacy of SEC was evaluated in a group of 221 patients with RA, resistant to MT therapy [153]. The patients were randomized into three groups (2:2:1), of which Group 1 (n = 88) received an i.v. "saturating" dose of SEC (10 mg/kg) upon enrolment, then a similar dose after 2 and 4 weeks, and after that SEC 150 mg, s.c., every 4 weeks; Group 2 (n = 89) were administered a "saturating" dose of 150 mg/week for 5 weeks, and then 150 mg once every 4 weeks; the patients in the PL group (n = 44) started SEC treatment after 16 weeks at 150 mg once every 4 weeks. In the compared groups, there were no significant differences in the efficacy of therapy as per ACR20. At the same time, when the patients who received SEC were united in one group, they demonstrated a significantly higher efficacy of SEC therapy compared to the PL patients ($p <0.05$), and these differences were evident after 1, 2, 3, 4 and 16 weeks. ACR50 and ACR70 response was low, but higher in the SEC therapy group than in the PL group: ACR50 response was 19.2% and 9.1% and ACR70 response was 7.9% and 2.3% in the SEC and PL groups, respectively. The decrease in activity as per DAS28-ESR and DAS28-CRP indices was expressed to a greater extent ($p <0.05$) against the background of the SEC therapy than in the PL group. It should be noted that there was a lack of significant differences in the efficacy of the SEC therapy, depending on the treatment regimen, viz. i.v. or s.c. injection of a saturating dose of SEC 150 mg. The efficacy of SEC as per other "secondary endpoints" (Health Assessment Questionnaire, HAQ), as well as the dynamics of the CRP level, was also higher than in the PL group ($p <0.05$).

A recent Phase II study evaluated the association between clinical efficacy of SEC (10 mg/kg, i.v., every 2 weeks) and carriage of the HLA-DRB1 allele [154]. This study is of great interest because there is evidence of the functional role of HLA-DRB1*SE (shared epitope) (a characteristic immunogenic RA marker) that determines the polarization of the immune response in Th17 type RA [155]. This study demonstrated a higher efficacy of SEC compared to PL in ACR20 response (87.1% and 25.0%, respectively) and positive dynamics of the DAS28 index after 28 weeks. However, there was no relation between the SEC efficacy and HLA-DRB1*04 carriage. At the same time, the authors believe that the role of HLA-DR SE carriage and seropositivity in the RF as possible predictors of the efficacy of SEC in RA cannot be ruled out. A more detailed analysis of the outcomes showed that the carriers of these alleles completely lacked the PL effect (mainly, the population of Russian patients), while in patients who did not have these alleles, there was an improvement in the disease activity both in the SEC group and the PL group. It is noteworthy that, according to experimental studies based on the transplantation of synovial tissue of RA patients to SCID mice, it turned out that SEC is effective only at a high content of CD3 + T cells in the synovial tissue [156].

Thus, the obtained data testify to the efficacy of subcutaneous injections of SEC in RA treatment, which served as the basis for planning Phase III studies. RCT REASSURE 1 is aimed at evaluating the efficacy of SEC 75 mg and 150 mg in comparison with PL in patients with active RA receiving a stable dose of MT (7.5-25 mg/week) resistant to the treatment with TNF-α inhibitors (NCT01377012). The duration of the RCT will be 2 years, 630 patients are planned to be included in the study. The "primary endpoint" will be the efficacy of therapy (ACR20 response) after 24 weeks, and the "secondary end-

points" include the HAQ dynamics, the progression of joint destruction according to the X-ray data and the frequency of the full therapeutic response (ACR70 response for 6 months). RCT NURTURE 1 (NCT01350804) has similar objectives (and the research plan). In this study, the comparison group will include patients who received abatacept, T-lymphocyte costimulatory blocker. Study will last 1 year and cover 548 patients. Patients who will have completed this study will be transferred to the open-label study (4 years) with an objective to assess the long-term efficacy and safety of SEC at doses of 75 mg and 150 mg (NCT01640938).

Behcet's disease

The data above, which indicate the prevalence of the Th1/Th17 type immune response in the case of BD, served as the basis for a 24-week Phase III RCT (NCT00995709) which included 118 patients treated with SEC or PL. The main clinical manifestations of BD in patients were posterior uveitis and panoveitis. However, this study did not prove the efficacy of SEC therapy. Other studies of SEC therapy for BD treatment were terminated prematurely. Interestingly, the INF therapy, the efficacy of which has been rigorously proven in BD treatment, led to a marked decrease in IL-17 (and other "pro-inflammatory" cytokines: IFNγ, IL-2, TNF-α and IL-6) in the ophthalmic fluid, as well as IL-17 synthesis by activated CD4 + T cells and RORγδ expression in Th17 cells [157].

Crohn's disease

Despite the theoretical substantiation of the fundamental role of the IL-23/IL-17 axis in the immunopathogenesis of Crohn's disease [158, 159], the Phase II RCT was prematurely discontinued due to the absence of a significant response and an increase in the frequency of infectious complications, primarily fungal [160, 161]. These data have not only clinical but also very great theoretical importance, since they draw attention to the fundamental role of Th17-cytokines, and especially IL-22, in protecting the organism from pathogenic infections and, in general, in maintaining immune homeostasis [162].

Safety and tolerability

The SEC safety profile has been carefully analyzed in a very large number of Phase II/III studies [163, 164]. P.J. Mease et al. [164] summarized the data from five Phase III RPCIs, which included patients with psoriasis (ERASURE, FIXTURE, SCULPTURE, FEATURE and JUNCTURE), as well as two Phase III RPCIs that included patients with PsA (FUTURE 1 and FUTURE 2). The average duration of SEC therapy was 299.8 days, and PL was administered for 105.7 days. A total of 3928 patients who received at least one infusion of SEC (3225 patient-years) were analyzed. In the group of patients who received SEC, there were 4 fatal cases: haemorrhagic stroke (n = 1), cardiogenic shock (n = 1), alcohol intoxication (n = 1), suicide (n = 1).

In most cases, ARs were mild or moderately severe. In general, the frequency of infectious complications in the course of SEC therapy was higher than in the PL groups. The most frequent AR was the development of upper respiratory tract infection. More often than in the control group, there were cases of mild candidiasis, which was reverted with anti-candida therapy or the patients recovered spontaneously. It is important that the intensity and severity of candidiasis infection in the course of SEC therapy were significantly lower than in the patients with genetic IL-17 defects. Development of neutropenia (grades II-III) was noted, but there was no correlation between the number of neutrophils and the risk of infection. The incidence of IBD, severe cardiovascular complications and malignant neoplasms was very low and did not differ from the control group. It is important that SEC therapy is not associated with the risk of developing tuberculosis infection, a characteristic complication arising from the treatment with TNF-α inhibitors.

Future directions

IL-17A blocking MoAbs, the first and so far the only officially registered prototype of which is SEC, are highly effective at least in treating three serious human IMIDs: psoriasis, PsA and AS. Introduction of SEC, and in the near future, other biological agents, blocking the effects of IL-17, is one of the major achievements of pharmacology and clinical medicine of the early XXI century. Considering the prospects for further research in this area, we should first of all focus on the general problems of the "taxonomy" of IMIDs' immunopathogenic mechanisms in terms of the prevailing types of immune response, characterized by a specific profile of cytokine synthesis at various (early, advanced or late) stages of the disease [165, 166]. It should be emphasized that IL-17 has multiple pathological effects cross-linking with other "pro-inflammatory" cytokines on different cellular populations [18, 70]. At first glance, it seems paradoxical, but although the cytokines of the IL-17 family have a wide (to a certain extent unique) range of "pro-inflammatory" and destructive effects, in RA cases IL-17A blocking MoAbs are less effective than inhibitors of other "pro-inflammatory" cytokines (TNF-α, IL-6). At the same time, with psoriasis, PsA and AS, IL-17A blocking MoAbs not only are not inferior to TNF-α inhibitors, but also even surpass them, and the IL-6 (clazacizumab) or its receptors (tocilizumab) blocking MoAbs are ineffective or only modestly affect musculoskeletal manifestations of PsA [167]. The reasons for this paradox are not completely clear. It is suggested that this may be due to the existence of certain IL-17-dependent subtypes of RA [92], the different roles of IL-17 cytokines at different stages of the disease (early and late) [71] and/or the existence of reciprocal feedbacks between IL-17A and other effects "pro-inflammatory" cytokines, primarily TNF-α. Indeed, there are numerous data indicating that IL-17A exhibits pronounced synergism with respect to "pro-inflammatory" and destructive activity with TNF-α [168, 169]. It is not surprising that the "double" blockade of IL-17 and TNF-α with the help of appropriate antibodies to these cytokines more effectively suppresses inflammation and destruction of joints in collagen arthritis in mice than a single agent therapy with either of them [170]. There is evidence that in some RA patients the increase in the number of Th17 cells and the concentration of IL-17 in the serum is associated with resistance to TNF-α inhibitors therapy [88, 89], and in the course of such treatment a paradoxical increase in the number of Th17 cells and the synthesis of p40 (a subunit of IL-12 and IL-23) are observed [89, 171, 172]. It seems that inhibition of TNF-α does not control the activation of the Th17-type immune response and can even promote it [173].

All this together creates prerequisites for the development of new approaches to IMID treatment related to the "double inhibition" of IL-17 and TNF-α using innovative biotechnological methods based on the "design" of so-called bispecific antibodies [174]. Preliminary data from experimental studies indicate that bispecific antibodies that bind IL-17 and TNF-α inhibit the synthesis of "pro-inflammatory" cytokines (IL-6,

IL-8, G-CSF) and MMPs in the culture of synovial fibroblasts stimulated by TNF-α and IL-17 to a greater extent than TNF-α and IL-17 blocking MoAbs separately [175]. In experiments on the arthritis model in TNF-transgenic mice, it was found that these antibodies effectively suppress inflammation and destruction of joints. At present, there are development and clinical studies on several IL-17/TNF-α bispecific antibodies, including ABT-122, that has a double variable immunoglobulin domain, one of the Fab fragments of which is directed against TNF-α and the other against IL-17; and COVA322, a recombinant molecule consisting of completely human antibodies to TNF-α and a high IL-17A affinity funomer (a small globular protein with a molecular mass of 7 kDa) [176].

Of particular interest are the developments of Russian scientists. BIOCAD (Russia's leading innovative biotechnology company) created BCD-121, bispecific MoAbs to TNF-α and IL-17. The preclinical studies of BCD-121 demonstrate the anti-inflammatory activity in vitro and in vivo, and the specific activity of BCD-121 against the TNF-α and IL-17 targets is 2-3 times higher than that of TNF-α blocking MoAbs (ADA) and IL-17 blocking MoAbs. Further study of the drug is planned for clinical trials.

Thus, IL-17 inhibition with SEC therapy is a breakthrough in the treatment of psoriasis and, probably, the most severe subtypes of PsA and AS. Even as we speak the most important clinical advantages of the SEC therapy - overcoming the resistance to TNF-α inhibitors - have been proven. Great progress has been made in deciphering the mechanisms of Th17-type immune response dysregulation. This creates prerequisites for improving the therapy of human IMIDs, which are pathogenically related to the activation of the IL-23/IL-17 axis and their spectrum is steadily expanding. However, there remain many unresolved problems, primarily due to the heterogeneity of the IMID immunopathogenesis mechanisms within endotypes (subtypes of the disease associated with various immunopathological mechanisms) of these diseases [166], which complicates the personalization of therapy both at the onset of the disease and as it advances. It is hoped that as the clinical experience of IMID pharmacotherapy with biological agents with various action mechanisms accumulates, not only the outcome of "severe" patients suffering from IMID will be improved, but also new facts will be obtained that will enable us to expand our understanding of the fundamental mechanisms of these disease pathogenesis.

Study transparency

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