Potential uses of upadacitinib in rheumatoid arthritis and other inflammatory rheumatic diseases

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The explanation of the mechanisms underlying the pathogenesis of rheumatoid arthritis (RA), along with the development of a wide range of genetically engineered biological disease-modifying anti-rheumatic drugs (bDMARDs), is among the major achievements of medicine in the 21st century. A new direction in the pharmacotherapy of inflammatory rheumatic diseases is associated with the development of "targeted" oral anti-inflammatory drugs, which include Janus kinase (JAK) inhibitors. One representative of the class of JAK inhibitors is upadacitinib (UPA), which has been registered for the treatment of RA and is undergoing clinical studies in patients with ankylosing spondylitis, psoriatic arthritis, and other inflammatory rheumatic diseases. This review presents new data on the efficacy and safety of UPA in RA.

Keywords: rheumatoid arthritis; JAK inhibitors; upadacitinib
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ПЕРСПЕКТИВЫ ПРИМЕНЕНИЯ УПАДАЦИТИНИБА ПРИ РЕВМАТОИДНОМ АРТРИТЕ И ДРУГИХ ИММУНОВОСПАЛИТЕЛЬНЫХ РЕВМАТИЧЕСКИХ ЗАБОЛЕВАНИЯХ

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Расшифровка механизмов патогенеза ревматоидного артрита в сочетании с разработкой широкого спектра генно-инженерных биологических препаратов относятся к числу крупных достижений медицины XXI в. Новое направление фармакотерапии иммуновоспалительных ревматических заболеваний связано с созданием «таргетных» пероральных лекарственных противовоспалительных препаратов, к которым относятся ингибиторы янус-киназ. Представителем класса этих ингибиторов является упадацитиниб, который зарегистрирован для лечения ревматоидного артрита и проходит клинические испытания при анкилозирующем спондилите, псориатическом артрите и других иммуновоспалительных ревматических заболеваниях. В обзоре представлены новые данные, касающиеся эффективности и безопасности упадацитиниба при ревматоидном артрите.

Ключевые слова: ревматоидный артрит, ингибиторы JAK, упадацитиниб
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The expansion of knowledge about the mechanisms underlying the pathogenesis of inflammatory rheumatic diseases, which stimulated the development of a wide range of new anti-inflammatory drugs, is among the major achievements of medicine in the 21st century [1, 2]. Among these drugs, Janus kinase (JAK) inhibitors occupy a special place [3, 4], as their introduction into clinical practice has significantly expanded the potential use of pharmacotherapy for rheumatoid arthritis (RA) and other inflammatory rheumatic diseases. Along with tofacitinib (TOFA) [5, 6] and baricitinib (BARI) [7, 8], the new JAK inhibitor, upadacitinib (UPA), was recently registered for the treatment of RA [9, 10]. Discussion of its potential future uses in rheumatology is the objective of our review.

Materials related to the molecular mechanisms that determine the anti-inflammatory and immunomodulatory effects of JAK inhibitors are summarized in a series of reviews [3, 4, 11, 12]. The pharmacological "target" for these drugs is a signaling pathway that includes type I and type II cytokine receptors, four JAKs (JAK1, JAK2, JAK3, and TYK 2 – tyrosine kinase 2), and seven STAT (signal transducer and activator of transcription) factors and regulates the transmission of intracellular signals from more than 50 cytokines, interferons (IFNs), and growth factors. Depending on the selectivity for JAK isoforms, drugs are conventionally subdivided into nonselective JAK (pan)inhibitors and selective JAK inhibitors. However, the selectivity of JAK inhibitors is relative, it does not always correspond to the expected clinical efficacy and the development of adverse drug reactions (ADRs) and depends on the dose of the drug ("therapeutic window" of selectivity), their ability to penetrate into cells, and genetic polymorphisms of the JAK [13–15]. Nevertheless, the data obtained with classical methods of pharmacological testing (suppression of the activity of recombinant JAKs, phosphorylation of STATs induced by cytokines in vitro, ex vivo in various cell lines, etc.) allow classification of UPA as a selective inhibitor of JAK1. According to the "enzymatic" method, UPA is more than 40 times more selective for JAK1 than for JAK2, 130 times more selective for JAK1 than for JAK3, and 190 times more selective for JAK1 than for TYK1 [16], while the "cellular" method shows that it inhibits the signaling of JAK1-dependent cytokines, in particular interleukin (IL) 6, IL2, interferon (IFN) γ, 60 times more strongly than JAK2-dependent cytokines (erythropoietin). UPA suppresses inflammation, synovial hypertrophy, cartilage destruction, and bone erosion when administered to rats with experimental arthritis.

The general pharmacological characteristics of UPA in comparison with TOFA and BARI are presented in table 1.

The efficacy of UPA

Phase I and II studies

A Phase I study in healthy volunteers demonstrated that UPA has a favorable safety profile at "supratherapeutic" doses of 48 mg and 24 mg twice daily for 14 and 27 days [18]. The pharmacokinetic profile of UPA is characterized by a short elimination half-life, no accumulation, and no interaction with methotrexate (MTX) [17].

Within the framework of Phase IIb, 2 randomized controlled trials (RCTs) (BALANCE-1 and BALANCE-2) were conducted. The former included patients resistant to therapy with tumor necrosis factor (TNF) α inhibitors [19], and the latter enrolled MTX-resistant patients [20]. Both studies evaluated the efficacy of UPA at doses of 3 mg, 6 mg, 12 mg, 18 mg twice daily. In addition, the BALANCE-2 study included patients who received UPA at a dose of 24 mg twice daily. In both studies, a primary endpoint of 20% improvement after 12 weeks (ACR20) compared with placebo (PL) was achieved; a very rapid development of the effect was noted (after 2 weeks); the effect showed a "plateau" in patients treated with UPA 6 mg and 12 mg twice daily.

Phase III studies

The Phase III research program for UPA (SELECT) includes 7 international RCTs (table 2); the SELECT-SUNRISE study was conducted only in Japan [27]. The RCTs included patients with active RA, the overwhelming majority of whom were seropositive for rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACCP). The patients had not previously received therapy with conventional disease-modifying antirheumatic drugs (cDMARDs), were resistant to MTX and other DMARDs, as well as genetically engineered biological DMARDS (bDMARDs). More than half the patients received low-dose glucocorticoid therapy (table 3).

Looking ahead, it should be emphasized that all RCTs achieved all planned primary and secondary endpoints: clinical, radiological, and functional, reflecting the quality of life of patients, as assessed with the HAQ-DI (Health Assessment Questionnaire Disability Index), FACIT-FATIGUE (Functional Assessment of Chronic Illness Therapy – fatigue scale), and SF-36 (Short Form-36) [29, 30]. Special attention should be paid to the materials of long-term extended studies (Long-Term Extension – LTE), which included patients who had completed respective RCTs and continued to take UPA in the form of monotherapy or combination therapy with DMARDs: SELECT-COMPARE (72 weeks) [31], SELECT-MONOTHERAPY (84 weeks) [32], SELECT-EARLY (72 weeks) [33]. There were no significant differences in the effectiveness of therapy between UPA doses of 15 mg (UPA 15 mg) and 30 mg (UPA 30 mg) once daily, but an increase in the risk of ADRs was observed with UPA 30 mg. Therefore, it was UPA 15 mg that was prescribed to patients with RA who entered the LTE and was officially registered for the treatment of RA. The data regarding the effectiveness of UPA in RCTs (Phase III) in patients with RA are summarized in table 4.

The RCTs SELECT-NEXT [21] and SELECT-BYOND [22] evaluated the efficacy of UPA 15 mg and 30 mg (in combination with conventional DMARDs) in patients with refractoriness to conventional DMARDs and bDMARDs, respectively. In both studies, the primary endpoints, namely the ACR20 and low activity (DAS28-CRP$\leqslant$3.2) effects, were achieved after 12 weeks of treatment with UPA (15 mg and 30 mg).

In particular, in the SELECT-NEXT study, the effect (ACR20) after 12 weeks was observed in 65% of patients (UPA 15 mg), in 66% of patients (UPA 30 mg), and in 36% of patients in the PL group ($p<0.001$), while the endpoint of DAS28-CRP $\leqslant$32 was achieved in 48%, 48%, and 17% of patients, respectively ($p<0.0001$).

In the SELECT-BEYOND study, which included the most severely ill populations of patients with RA (refractoriness to treatment with one or more bDMARDs), a rapid improvement in RA activity was observed with UPA 15 mg and UPA 30 mg. After 12 weeks, the effect (ACR20) was observed in 65% of patients (UPA 15 mg), 56% of patients (UPA 30 mg), and only 28% of patients in the PL group ($p<0.0001$), whereas low activity (DAS28-CRP$\leqslant$3.2) was seen in 43%, 42%, and 14% of patients ($p\leqslant0.0001$), respectively.

The SELECT-EARLY [23, 33] and SELECT-MONOTHERAPY [25] studies were undertaken to analyze

Table 1. Comparative pharmacological characteristics of upadacitinib, tofacitinib, and baricitinib

	Upadacitinib (Rinvoq)	Tofacitinib (Xejjanz)	Baricitinib (Olumiant)
JAK inhibition	JAK1	JAK1>JAK3>JAK2>TYK2	JAK1=JAK2
Dose	15 mg once daily	5 mg twice daily	2 mg once daily
Approved indications	Rheumatoid arthritis	Rheumatoid arthritis	Rheumatoid arthritis Psoriatic arthritis Ulcerative colitis
Approval	FDA – 2019 EMA – 2019 Russia – 2020	FDA – 2012 EMA – 2017 Russia – 2016	FDA – 2018 EMA – 2017 Russia – 2019
Registration	Not known	More than 80 countries	More than 50 countries
Pharmacokinetics	T_{max} 2–4 hrs; $t_{1/2}$ 8–14 hrs	T_{max} 0.5–1 hrs; $t_{1/2}$ 3.3 hrs	T_{max} 2–4 hrs; $t_{1/2}$ 8–14 hrs
IC50	IC50JAK1 45 nM IC50JAK2 109 nM IC50JAK3 2.1 μM IC50TYK2 4.7 μM	IC50JAK1 3.2 nM IC50JAK2 4.2 nM IC50JAK3 1.6 nM IC50TYK2 34 nM	IC50JAK1 5.9 nM IC50JAK2 5.7 nM IC50JAK3 420 nM IC50TYK2 60 nM
Drug interactions	CYP3A4 inhibitors (ketoconazole) and inducers (rifampicin)	CYP3A4 inhibitors (ketoconazole)	OAT3 and CYP3A4 inhibitors (ketoconazole) and inducers (rifampicin)
Renal failure	No dose adjustment is required for mild/moderate CRF. Data for severe CRF are missing	No dose adjustment is required for mild (CC of 50–89 mL/min) and moderate (CC of 30–49 mL/min) CRF. In case of severe CRF (CC <30 mL/min) the dose should not exceed 5 mg a day	1 mg once daily if CC is 30–60 mL/min. Not recommended if CC is <30 mL/min
Hepatic failure	No dose adjustment is required for mild (Child Pugh A) and moderate (Child Pugh B) hepatic failure. Not recommended in case of severe hepatic failure (Child Pugh C)	No dose adjustment is required for mild (Child Pugh A) hepatic failure. In case of moderate (Child Pugh B) hepatic failure the recommended dose is 5 mg a day Not recommended in case of severe hepatic failure (Child Pugh C)	No dose adjustment is required for mild (Child Pugh A) and moderate (Child Pugh B) hepatic failure. Not recommended in case of severe hepatic failure (Child Pugh C)
ADR	Common: upper respiratory tract infection (colds, sinusitis), nausea, cough, and fever. Rare: severe infections, cancers, thrombosis, gastrointestinal perforations, impaired laboratory parameters, and embryofetal toxicity. Very rare: cardiovascular disasters	Common: upper and lower respiratory tract infection, HZ infection, urinary tract infection, nausea, vomiting, abdominal pain, gastritis, rash, weight gain, anemia, leukopenia, and elevated hepatic transaminases Rare: tuberculosis, diverticulitis, pyelonephritis, cellulitis, viral gastroenteritis, and increased creatinine, cholesterol, and LDL levels.	Frequent: upper and lower respiratory tract infection, HZ infection, urinary tract infection, pneumonia, thrombocytosis Rare: leukopenia, elevated CPK, increased level of triglycerides, and weight gain.
Clinical study program	PsA – Phase III AS – Phase II UC – Phase III CD – Phase III GCA – Phase III AD – Phase I JIA – Phase I	SpA – Phase IV Psoriasis – Phase III JIA – Phase III SLE – Phase II CD – Phase II Alopecia areata – Phase IV Uveitis – Phase II Scleritis – Phase II DLE – Phase II DM – Phase I SS – Phase I	AD – Phase III Alopecia – Phase III SLE – Phase III JIA – Phase III Psoriasis – Phase II GCA – Phase II

Note: CC, creatinine clearance; CRF, chronic renal failure; PsA, psoriatic arthritis; AS, ankylosing spondylitis; SpA, spondyloarthritis; UC, ulcerative colitis; CD, Crohn's disease; JIA, juvenile idiopathic arthritis; AD, atopic dermatitis; GCA, giant cell arteritis; SLE, systemic lupus erythematosus; DLE, discoid lupus erythematosus; DM, dermatomyositis; SS, systemic scleroderma; CS, cholesterol; TG, triglycerides; LDL, low density lipoprotein; HZ – herpes zoster; IC50, half-maximal inhibitory concentration; T_{max}, time to peak plasma concentration; $t_{1/2}$, elimination half-life.

the efficacy of UPA monotherapy in patients who did not receive MTX (early RA) and were resistant to MTX, respectively. Patients received MTX as an active "comparator" in the reference groups of both studies.

SELECT-EARLE [23, 33] included patients with risk factors for an unfavorable prognosis (⩾1 erosions in small joints of the hands on X-ray examination, positive tests for RF and ACCP), who were randomized into 3 groups: UPA 15 mg, UPA 30 mg, and MTX. The SELECT-EARLY study consisted of 2 phases. During stage 1 (48 weeks), an RCT was carried out to compare the efficacy of monotherapy with UPA (15 mg and 30 mg) and MTX (dose titration up to 20 mg/week for 8 weeks). Stage 2 (duration up to 4 years) was an LTE, during which patients received open-label therapy with the addition (rescue therapy) of UPA or MTX for patients who had not achieved remission (CDAI ⩽2.8). Among 945 randomized patients, 781 (83%) completed stage 1. After 24 weeks, the efficacy of therapy (ACR50) was 52.1% and 56.4% in the UPA 15 mg and 30 mg groups, respectively, while in the control group (MTX) it was 28.3%; the endpoint of DAS28-CRP ⩽2.6 (clinical remission) was achieved in 48.3%, 50.0%, and 18.5% of patients, respectively ($p \leqslant 0.001$, in all cases). As can be seen from **table 5,** treatment with UPA 15 mg and 30 mg was associated with

Table 2. General characteristics of RCTs (phase III) of upadacitinib in rheumatoid arthritis

	SELECT-EARLY [23]	SELECT-NEXT [21]	SELECT-MONOTHERAPY [25]	SELECT-COMPARE [24, 28]	SELECT-BYOND [22]	SELECT-CHOICE [26]
Population	MTX-naïve	DMARD-refractory	MTX-refractory	MTX-refractory	GEBP-refractory	GEBP-refractory
Number of patients	1002	661	648	1629	499	657
Background therapy	No	DMARDs	No	MTX	DMARDs	DMARDs
UPA, doses (single)	7.5 mg, 15 mg, 30 mg a day	15 mg, 30 mg a day	15 mg, 30 mg a day	15 mg a day	15 mg, 30 mg a day	15 mg a day
Reference product	MTX	PL	MTX	PL, ADA	PL	ABC
Primary Endpoints	ACR20/50 DAS28-CRP ≤2.6 (12 wks);	ACR20 DAS28-CRP ≤3.2 (12 wks)	ACR20 DAS28-CRP ≤3.2 (14 wks)	ACR20 DAS28-CRP ≤2.6 (12 wks)	ACR20 DAS28-CRP ≤3.2 (12 wks)	DAS28-CRP changes (12 wks, non-inferiority)
Duration of the main study period	48 wks	12 wks	14 wks	48 wks	24 wks	24 wks
Assessment of radiographic progression	mTSS (24 wks)	No	No	mTSS (26 wks)	No	No

Note: mTSS, modified total Sharp score; UPA, upadacitinib; MTX, methotrexate; ABC, abatacept; ADA, adalimumab; PL, placebo; GEBP, genetically engineered biological preparations; DMARDs, disease-modifying antirheumatic drugs; DAS, Disease Activity Score; ACR, American College of Rheumatology; CRP, C-reactive protein.

Table 3. General characteristics of patients with rheumatoid arthritis in RCTs (phase III) of upadacitinib

	SELECT-EARLY [23]	SELECT-NEXT [21]	SELECT-MONOTHERAPY [25]	SELECT-COMPARE [24, 28]	SELECT-BYOND [22]	SELECT-CHOICE [26]
Age, yrs (SD)	51.9 (12.88)	55.3 (11.47)	54.5 (12.20)	54.2 (12.08)	56.3 (11.34)	55.8 (11.44)
Male, %	24	17.6	19.8	20.0	16.5	17.8
RA duration, mean (SD)	2.9 (5.38)	7.3 (7.89)	7.5 (8.88)	8.1 (7.73)	12.4 (9.38)	12.4 (9.49)
TJC, mean (SD)	25.4 (14.42)	25.2 (13.80)	24.5 (15.10)	26.4 (15.15)	27.8 (16.31)	23.9 (13.77)
SJC, mean (SD)	17 (10.75)	16.0 (10.04)	16.4 (10.94)	16.6 (10.31)	17.0 (10.75)	14.2 (7.60)
DAS28-CRB, mean (SD)	5.9 (0.97)	5.7 (0.97)	5.6 (0.92)	5.8 (0.97)	5.9 (0.95)	5.7 (0.90)
RF +, %	79.7	73.8	71.4	80.9	73	62.4
Anti-CCP +, %	81.4	79.1	73.3	80.6	72.6	
History of GEBP administration, %	no	12.2	no	no	100	100
History of GEBP ineffectiveness, %	no	no	no	no		
- 1 MoA and ≤ 2 GEBP					70.7	68.8
> 1 MoA and > 2 GEBP					29.3	32.2
Administration of GC, %	46.06	43.3	51.61	59.6	50.6	55.8
GC dose, mean (SD)	6.4 (3.10)	6.0 (2.36)	6.1 (2.52)	6.2 (2.27)	5.37 (2.37)	6.1 (2.50)
History of DMARD administration	No		No	No		Not available
- MTX only, %		55.5			73.3	
- MTX + other DMARDs, %		21.4			11.8	
- Other DMARDs		23.3			1 4.9	
Administration of MTX during RCT, %	No	76.5	100	100	no	Not available
MTX dose, mean (SD)		17.0 (4.87)	16.8 (4.21)	17.0 (4.17)		Not available

Note: MoA, mechanism of action; TJC, tender joint count; SJC, swollen joint count; SD, standard deviation.

a stable, statistically significant decrease in RA activity (compared with MTX monotherapy) up to 72 weeks.

In addition, among patients who achieved ACR50 improvement at 12 weeks, significantly more patients treated with UPA (15 mg and 30 mg) had a ⩾50% improvement in 5 ACR components, including pain, physician global assessment, patient global assessment, HAQ-DI, and CRP, as compared with the MTX group [34].

Important results were obtained in the SELECT-EARLY sub-analysis, which assessed the efficacy of UPA and MT in a group of patients with RA (n=270) who were administered the drugs very early (within 90 days of diagnosis) [35].

As can be seen from **table 6,** early initiation of UPA therapy is associated with a high incidence of remission (including Boolean remission) and suppression of joint destruction. In fact, SELECT-EARLY is one of the few studies that has demonstrated the benefits of "alternative" anti-inflammatory therapy, as compared with high doses of MTX, in patients with early RA.

The SELECT-MONOTHERAPY study [25] included 648 patients who were randomized into 3 groups: monotherapy with UPA 15 mg, UPA 30 mg, and MTX. After 14 weeks, treatment was effective (based on ACR20) in 68%, 71%, and 41% of patients in the UPA 15 mg, UPA 30 mg, and MTX groups, respectively; based on the DAS28-CRP<3.2 criterion, the respective percentages were 45%, 53%, and 19%, respectively (p<0.001, in all cases). Within the LTE program, patients receiving MTX were switched to UPA therapy (15 mg or 30 mg) after 14 weeks [32]. As can be seen from table 7, the efficacy of therapy in patients switched from MTX to UPA 15 mg and 30 mg was the same as in patients initially administered UPA.

Comparison of SELECT-MONOTHERAPY and SELECT-NEXT data is of interest, as they demonstrate no

Table 4. Effectiveness of upadacitinib in rheumatoid arthritis (based on Phase III RCTs)

	ACR20	ACR50	ACR70	Low activity (DAS28-CRB ≤3.2)	Remission (DAS28-CRB ≤2.6)
SELECT-COMPARE (at Week 12)					
UPA + MTX (*n*=651)	71%	45%	26%	49%	29%
ADA + MTX (*n*=327)	63%*	29%**	15%**	29?**	18%**
PL (*n*=651)	36%**	15%**	5%**	14%**	6%**
SELECT-NEXT (at Week 12)					
UPA (*n*=221)	64%	38%	21%	48%	31%
PL (*n*=221)	36%**	15%**	6?**	17%**	10%**
SELECT-MONOTHERAPY (14 weeks)					
UPA (*n*=217)	68%	42%	23%	45%	28%
MTX (*n*=216)	41%**	15%**	3:**	19%**	8%**
SELECT-BEYOND (12 weeks)					
UPA + DMARDs (*n*=169)	65%	34%	12%	43%	29%
PL + DMARDs (*n*=164)	28%**	12%**	7%**	14%**	10%**
SELECT- CHOICE (12 weeks)					
UPA + DMARDs (*n*=303)	75.6%	46.2%	21.5%	49.8%	30.0%
ABC + DMARDs (*n*=309)	66.3%*	34.3%***	13.6%***	28.8%**	12.3%**

Note: * $p \leq 0.05$; ** $p \leq 0.001$; *** $p \leq 0.01$.

Table 5. The efficacy of UPA therapy according to the SELECT-EARLY study

Parameters	24 weeks			72 weeks		
	MTX	UPA, 15 mg	UPA, 30 mg	MTX	UPA, 15 mg	UPA, 30 mg
ACR20, %	59	78***	79***	50	71***	72***
ACR50, %	33	60***	66***	39	62***	67***
ACR70, %	19	45***	50***	26	47***	54***
DAS28-CRP ≤3.2				38	63***	69***
DAS28-CRP ≤2.6	19	48***	50***	28	52***	61***
CDAI ≤10.0, %	38	56***	61***	42	60***	69***
CDAI ≤2.8, %	11	28***	20***	19	35***	44***
SDAI ≤11.0, %	37	57***	60***			
SDAI ≤3.3, %	9	28***	30***			
Boolean remission	7	24***	25***	13	29***	33***

Note: *** $p<0.0001$.

Table 6. The efficacy of upadacitinib and methotrexate in early rheumatoid arthritis

Parameters	MTX (*n*=99)	UPA, 15 mg (*n*=98)	UPA, 30 mg (*n*=73)
ACR20, %	63	85***	84**
ACR50, %	35	66***	75***
ACR70, %	22	49***	62***
DAS28-CRP ≤3.2, %	34	64***	65***
DAS28-CRP ≤2.6, %	20	55***	60***
CDAI ≤10, %	42	59*	69***
CDAI ≤2.8, %	11	35***	40***
Boolean remission, %	7	34***	37***
No progression of joint destruction, %	66	83*	95***

Note: * $p<0.05$, ** $p<0.001$; *** $p<0.001$.

statistically significant differences in the efficacy of UPA monotherapy and combination therapy with UPA and conventional DMARDs [36] (table 8).

In the long term, these data may be very important for optimizing the treatment of patients with RA who develop ADRs or are intolerant to conventional DMARDs, primarily MTX.

SELECT-COMPARE [24, 28] is the largest RCT within the SELECT program (*n*=1629), which included patients resistant to MTX therapy. The objective of this study was to compare the efficacy of UPA and monoclonal antibodies (mAbs) to tumor necrosis factor (TNF) α, adalimumab (ADA). The patients were randomized into 3 groups: UPA 15 mg, ADA (40 mg every 2 weeks) and PL. After 12 weeks, the efficacy of UPA significantly exceeded that of PL according to ACR20 (72% vs. 36%) and DAS28-CRP ⩽2.6 (29% vs. 6%) responses ($p<0.0001$, in both cases). There was a higher efficacy of UPA compared to ADA according to ACR50 (45% vs. 29%; $p<0.001$) and DAS28-CRP⩽3.3 (45% vs. 29%; $p<0.001$) responses. After 26 weeks, patients with insufficient efficacy of ADA were switched to UPA, and vice versa. Replacing one drug with the other led to an increase in the efficacy of therapy (the number of patients who achieved CDAI⩽10), and it was more noticeable when replacing ADA with UPA (53%) than with the UPA to ADA switch (41%) [37]. Data from the LTE SELECT-COMPARE [31] confirm a higher long-term efficacy (72 weeks) of combination therapy with UPA and MTX as compared with ADA in combination with MTX (table 9).

Table 7. The efficacy of upadacitinib and methotrexate therapy (SELECT-MONOTHERAPY)

Parameters	MTX → UPA 15 mg	MTX → UPA 30 mg	UPA, 15 mg	UPA, 30 mg
ACR20, %	86	90	88	96
ACR50, %	71	68	71	78
ACR70, %	49	50	54	66
DAS28-CRP ≤2.6, %	56	63	60	77
DAS28-CRP ≤3.2, %	80	79	76	85
CDAI ≤10, %	78	85	74	85
CDAI ≤2.8, %	38	29	34	49
Boolean remission, %	27	23	26	41

Analysis of the data from the SELECT-EARLY and SELECT-COMPARE studies revealed that UPA monotherapy or combination therapy with UPA suppresses the progression of

Table 8. Comparative efficacy of upadacitinib monotherapy (SELECT-MONOTHERAPY) and combination therapy with upadacitinib and conventional DMARDs (SELECT-NEXT)

Parameters	UPA monotherapy (14 weeks) SELECT-MONOTHERAPY			Combination treatment with UPA and conventional DMARDs (12 weeks) SELECT-NEXT			*p* (monotherapy vs. combination therapy)	
	MTX (*n*=216)	UPA, 15 mg (217)	UPA, 30 mg (215)	PL + MTX (*n*=165)	UPA 15 mg + MTX (*n*=148)	UPA 30 mg + MTX (*n*=153)	UPA, 15 mg	UPA, 30 mg
ACR20, %	41.2	67.7	71.2	38.2	66.2	65.4	0.962	0.561
ACR50, %	15.3	41.9	52.1	16.4	41.2	43.1	0.578	0.217
ACR70,%	2.8	22.6	33.0	4.8	20.9	26.1	0.172	0.134
DAS28-CRP ≤3.2, %	19.4	44.7	53.5	18.2	48.6	49.7	0.564	0.878
DAS28-CRP ≤2.6, %	8.3	28.1	40.9	9.7	28.4	30.7	0.594	0.142
CDAI ≤10, %	24.5	34.6	46.5	20.6	41.2	43.8	0.164	0.661
CDAI ≤2/8, %	0.9	12.9	19.5	3.0	9.5	13.7	0.063	0.069
HAQ-DI change from baseline	-0.22	-0.56	-0.63	-0.32	-0.61	-0.60	0.593	0.108

joint destruction to a greater extent than MTX monotherapy or combined ADA and MTX therapy [38] (table 10).

A pooled analysis of the results of 3 RCTs (SELECT-NEXT, SELECT-BYOND, SELECT-COMPARE) suggests that the efficacy of UPA therapy (15 mg and 30 mg) in combination with conventional DMARDs does not depend on the baseline characteristics of patients, including gender, age, body weight, duration of illness, seropositivity for RF and ACCP, and CRP concentration [39].

Recently, materials from the RCT SELECT-CHOICE were presented [34]; they analyzed the comparative efficacy of UPA and the T-lymphocyte co-stimulation blocker abatacept (ABC). It should be reminded that ABC is a very effective and safe DMARD [40] non-inferior to ADA in terms of efficacy [41]. The study included 612 patients resistant to one (67%) or several DMARDs, including 303 patients treated with UPA (15 mg) and 309 patients receiving ABC (standard dose, intravenous). As can be seen from table 11, UPA was significantly superior to ABC at 12 and 24 weeks in terms of all standard efficacy parameters.

The patient-reported outcome (PRO) is an essential indicator of treatment efficacy in patients with rheumatoid arthritis [42]. Data from the SELECT-NEXT and SELECT-BEYOND studies demonstrated that UPA is superior to PL in terms of such PRO parameters as pain, physical performance (HAQ-DI), fatigue (FACIT-F), and quality of life (SF-36) [29, 30]. According to the data from the RCT SELECT-NEXT, UPA treatment (compared to PL) very quickly (during the first week) leads to a decrease in morning stiffness ($p<0.0001$), and these differences persist for 12 weeks [21, 29]. In the RCT SELECT-COMPARE, UPA was superior to ADA in terms of the effect on the pain index (–32.1 vs. –25.6, respectively, $p\leqslant0.001$) and HAQ-DI improvement (–0.60 vs. –0.49, respectively, $p\leqslant0.01$) within 48 weeks [31].

The safety of UPA

The safety profile of UPA was assessed during in the pooled analysis of the RCTs SELECT-NEXT, SELECT-BYOND, SELECT-EARLY, SELECT-MONOTHERAPY, and SELECT-COMPARE [43], which included 3833 patients who received ⩾1 dose of UPA, including 2630 subjects who received UPA 15 mg and 1204 patients administered UPA 30 mg. Adverse drug reactions were assessed using exposure-adjusted event rates (EAERs) per 100 person-years (PYs). The incidence of severe and opportunistic infections [44, 45] and venous thrombosis [46] was analyzed separately. The most common ADRs (⩾5 ADRs / 100 PYs) in patients receiving UPA (15 mg) were nasopharyngitis (NP), upper respiratory tract infection (URTI), bronchitis, urinary tract infection (UTI), increased concentrations of creatine phosphokinase (CPK) and aspartate aminotransferase (AST); in patients treated with UPA 30 mg, the most common ADRs included URTI, UTI, increase in CPK, NP, bacterial bronchitis, and HZ infection. In general, the incidence rates of ADRs and ADRs leading to interruption of treatment with UPA 15 mg, MTX, and ADA were similar, and the number of ADRs was higher in patients receiving UPA 30 mg than in those administered UPA 15 mg. The incidence of HZ infection was higher in the groups of patients treated with UPA (15 mg and

Table 9. The long-term (72 weeks) efficacy of upadacitinib and adalimumab (SELECT-COMPARE)

Parameters	UPA 15 mg + MTX (*n*=651)	ADA + MTX (*n*=327)
ACR20, %	64*	53
ACR50, %	51**	38
ACR70, %	38**	25
DAS28-CRP ≤2.6	41**	26
DAS28-CRP ≤3.2	49**	32

Note: * $p\leq0.01$; ** $p\leq0.001$.

Table 10. Effect of UPA and ADA therapy on the progression of joint destruction compared with PL (96 weeks)

Parameters	SELECT-EARLY			SELECT-COMPARE		
	UPA, 30 mg (*n*=231)	UPA, 15 mg (*n*=238)	MTX (*n*=186)	UPA, 15 mg MTX (*n*=327)	PL + MTX → UPA + MTX (*n*=529)	ADA + MTX (*n*=125)
No progression of joint destruction, %	91	89	76	82	77	75

Table 11. The efficacy of upadacitinib and abatacept (SELECT-CHOICE)

Parameters	12 weeks		24 weeks	
	UPA, 15 mg (*n*=303)	ABC (*n*=309)	UPA, 15 mg (*n*=303)	ABC (*n*=309)
ACR20, %	75.6*	66.3	78.9	73.8
ACR50, %	46.2*	34.3	59.4*	49.5
ACR70, %	21.5**	13.6	37.3**	26.5
DAS28-CRP≤2.6	30.0***	13.3	45.9***	31.4
DAS28-CRP≤3.2	49.8***	28.8	62.7***	47.9

Note: * $p\leq0.05$; ** $p\leq0.01$; *** $p\leq0.001$.

30 mg) than in the ADA and MTX groups. In the overwhelming majority of cases (95%), the course of HZ infection was mild. However, according to K. Winthrop et al. [45], although the incidence of HZ infection was higher in patients treated with UPA 30 mg than with UPA 15 mg, in the entire group it was comparable with the frequency of infection in patients treated with ADA in combination with MTX or MTX alone. Risk factors for HZ infection included a history of this infection, Asian residence ($p \leqslant 0.01$), and age ⩾65 years. The incidence of venous thrombosis (0.3–0.5 / 100 PYs), as well as cardiovascular complications and malignant neoplasms, was similar to the incidence of these complications in the MTX+ADA and MTX monotherapy groups, with the exception of a slight increase in the incidence of non-melanoma skin cancer in patients receiving UPA 30 mg. The risk factors for venous thrombosis in the presence of UPA were a history of these complications and high body mass index [46]. In total, 6 cases of tuberculosis were detected: 3 in patients receiving UPA 15 mg, 2 in the UPA 30 mg group, and 2 in the ADA group. The death rate (n=45) did not differ from that in the general population; in most cases deaths were due to cardiovascular complications.

Data from meta-analyses

The efficacy and safety of UPA assessed in comparison with other JAK inhibitors and bDMARDs [46–58] have been confirmed in a series of meta-analyses and systematic reviews. In particular, a network meta-analysis reported by J. Pope et al. [56], which included materials from the main RCTs of TOFA [59–62], the RCTs of BARI [63–65], and the RCTs of UPA [21, 24, 25, 27], yielded the following results. When assessed by parameters such as ACR50 and clinical remission (DAS28-CRP⩽2.6) after 12 weeks, combination therapy with UPA 15 mg and DMARDs (43.4% and 29.8% of patients, respectively) was found to be more effective than TOFA 5 mg (38.7% and 24.3% of patients, respectively), BARI 2 mg (37.1% and 20.1% of patients, respectively), and BARI 4 mg (36.7% and 22.8% of patients, respectively). Similar trends were obtained in the ACR50/70-based efficacy analysis after 24 weeks. The efficacy (ACR50) of UPA monotherapy (in 38.5% of patients) was higher than that of TOFA monotherapy (in 18.3% of patients). It should be emphasized that the differences in efficacy between the JAK inhibitors were quantitative and statistically insignificant. However, preliminary results of the analysis using the Matching-Adjusted Indirect Comparison (MAIC) method based on treatment efficacy adjustment depending on the clinical and demographic characteristics of patients (age, gender, numbers of swollen and tender joints, CRP, etc.) indicate that UPA has a higher efficacy compared with TOFA [58]. After 3 months, monotherapy with UPA was more effective (ACR70) than combination therapy with TOFA+MTX (with a difference of 9.9%, p<0.05), and combination therapy with UPA+MTX was more effective (ACR50) than combination therapy with TOFA+MTX (with a difference of 12.9%, p<0.05). After 6 months, a higher efficacy of the combination therapy with UPA+MTX was noted, as compared with TOFA+MTX, in terms of the following activity indices: SDA (difference 9.1%, p<0.05). CDAI (difference 7.5%, p<0.05), and DAS28-ESR (difference 11.3%, p<0.01).

K. Bechman et al. [66] conducted a meta-analysis of the incidence of infectious complications, including HZ infection, based on 21 RCTs, including 11 RCTs of TOFA (n=5888), 6 RCTs of BARI (n=3520), and 4 RCTs of UPA (n=1736). The incidence rate ratio (IRR) of severe infectious complications was 1.97 for TOFA (95% CI: 1.41–2.68), 3.16 for BARI (95% CI: 2.02–4.63), and 3.02 for UPA (95% CI: 0.98–7.04). The differences in IRR values for TOFA (1.22, 95% CI: 0.60–2.45), BARI (0.80, 95% CI: 0.46–1.38), and UPA (1.14, 95% CI 0.24–5.43) and PL were not statistically significant. The HZ infection IRR was 2.58 for TOFA (95% CI: 1.87–3.30), 3.16 for BARI (95% CI: 2.07–4.63), and 2.41 for UPA (95% CI: 0.66–6.18). The IRR was 2.86 (95% CI: 1.26–6.50) for BARI compared with PL, 1.38 (95% CI: 0.66–2.88) for TOFA, and 0.78 (95% CI: 0.19–3.22) for UPA. Thus, the incidence of infections during treatment with JAK inhibitors in patients with RA was very low; however, the risk of developing HZ infection (3.22 per 100 PYs) was higher than in the general population. There was a trend towards a higher risk of HZ infection with BARI than with the other JAK inhibitors, but these differences were not statistically significant.

The data of EULAR meta-analyses indicating similar efficacy and safety of bDMARDs and JAK inhibitors [47, 48] led to inclusion of UPA in the treatment algorithm for RA as a first line drug following lack of efficacy of DMARDs, primarily MTX [67].

Ankylosing spondylitis (AS)

UPA has been shown to be effective in patients with active AS (based on the modified New York criteria) not treated with bDMARDs, following an inadequate effect (intolerance) of at least two non-steroidal anti-inflammatory drugs (NSAIDs) [68, 69]. The RCT SELECT-AXIS 1 (duration 14 weeks) included 197 patients, among whom 93 patients received UPA (15 mg) and 94 patients received PL. The change in ASAS40 (Assessment in SpondyloArthritis international Society 40%) response after 12 weeks was used as the primary endpoint. Significantly more patients treated with UPA (52%) achieved the ASA40 response compared with the PL group (26%) (p=0.0003). Post-hoc analysis of the materials of this study found that UPA treatment is significantly superior to PL in terms of influence on quality of life indicators, including ASAS HI (Assessment in SpondyloArthritis international Society Health index) and ASQoL (Ankylosing Spondylitis quality of life) [69]. For example, after 14 weeks ASAS HI normalization (score ⩽5) was observed in 44.6% of patients in the UPA group and only in 21.1% of patients in the PL group (p<0.05). The minimal clinically important difference (MCID) in terms of ASAS HI change occurred in 44.7% of UPA-treated patients and in 27% of patients in the PL group (p<0.05); in terms of ASQoL, it was observed in 61.4% and 43% of patients, respectively (p<0.05). A rapid improvement in the quality of life parameters was characteristic; it was observed as early as after 4 weeks of therapy.

Psoriatic arthritis (PsA)

In the SELECT-PSA-1 RCT, the efficacy and safety of UPA compared with ADA and PL was assessed in 1705 patients with active PsA [70], 82% of whom had received MTX or other conventional DMARDs with insufficient effect. The patients were randomized into 4 groups (1:1:1:1): UPA 15mg (n=429), UPA 30 mg (n=423), ADA (n=429), and PL (n=423). The primary endpoint was the ACR20 response at 12 weeks. It was found that UPA treatment is associated with a decrease in PsA activity. The response (ACR20) was observed in 70.6% of patients who received UPA 15 mg, in 78.5% of patients administered UPA 30 mg, and only in 36% of patients in the PL group

(p<0.01 for UPA 15 mg and 30 mg vs. PL) and in 65% of patients in the ADA group (p<0.01 vs. UPA 15 and 30 mg). A higher efficacy of UPA (15 and 30 mg) was observed, as compared with PL and UPA 30 mg, compared with ADA, in the analysis of secondary endpoints (ACR50/70), as well as based on the DAQ-DI and pain changes (only UPA 30 mg). After 24 weeks, UPA-treated patients had a more pronounced slowdown in the progression of joint destruction (mTSS) compared with the PL group (p<0.001). The incidence of ADRs did not differ in patients receiving UPA 15 mg, ADA, or PL, but was moderately increased in patients receiving UPA 30 mg.

The SELECT-PSA-2 RCT included an analysis of the efficacy of UPA in PsA patients resistant to bDMARDs [71]. The study included 641 patients (54.3% women, mean duration of disease 10.1 years). 61% of the patients were resistant to 1 bDMARD, 18% were resistant to 2 bDMARDs, and 13% were resistant to 3 or more bDMARDs. The patients were randomized into 3 groups (1:1:1): UPA 15 mg (n=211), UPA 30 mg (n=218), and PL (n=212). After 12 weeks, the ACR20 response was 59.5%, 63.8%, and 24.1% in the compared groups, respectively (p<0.0001 for both comparisons). UPA was superior to PL in the analysis of secondary endpoints, including the ACR50/70 response and HAQ-DI, SF-36, FACIT-F, SAPS (Self-Assessment of Psoriasis Symptoms) changes. As in the previous studies, the incidence of ADRs in the UPA 15 mg and PL groups did not differ and was higher in patients treated with UPA 30 mg.

Perspectives

The data obtained in the process of large-scale RCTs within the SELECT program indicate that UPA, a "targeted" oral bDMARD, has been duly added to the pharmacotherapy armamentarium for RA (and possibly also other inflammatory rheumatic diseases); its common use in the future may contribute to a change in the paradigm of pharmacotherapy for this disease. Here are some facts confirming this position.

UPA therapy in early RA (SELECT-EARLY) was shown to have a high efficacy significantly superior to that of MTX monotherapy, which is considered the "gold standard" of treatment for this disease [67, 72]. These data allow discussion of the potential use of UPA as the "first" bDMARD, particularly in patients with very high RA activity at the onset of the disease and in whom optimal doses of MTX cannot be prescribed. However, in view of the data on the high efficacy and good tolerability of subcutaneous (s.c.) MTX (compared to the oral formulation of the drug) [72], especially in combination with glucocorticoids, it is advisable to conduct special RCTs devoted to comparing the efficacy and safety of UPA monotherapy and MTX monotherapy (s.c.) or in combination with glucocorticoids ("bridge" therapy). Taking into account the EULAR recommendations on the advisability of prescribing combination therapy with MTX and glucocorticoids in all patients with early RA as part of the "treatment to goal" strategy, a natural question arises about the advantages of "bridge" glucocorticoid therapy in patients for whom initiation of UPA therapy is planned. On the other hand, given the unfavorable consequences of long-term glucocorticoid therapy, primarily those associated with the development of ADRs [73], the possibility of reducing the dose or discontinuing glucocorticoid therapy during treatment with UPA in patients with advanced RA deserves special analysis. This is particularly important since 40–60% of patients who participated in the SELECT program received glucocorticoid therapy at an average dose of >6 mg/day (table 3). It should be emphasized that the problem of optimizing glucocorticoid therapy in rheumatology has become especially relevant during the coronavirus disease 2019 (COVID-19) pandemic, since glucocorticoid therapy is one of the risk factors of severe disease [74].

Since one third of patients with advanced RA have poor adherence to MTX treatment due to insufficient efficacy, development of ADRs, or poor subjective tolerance [75–77], the data on the effectiveness of UPA monotherapy (SELECT-MONOTHERAPY), which does not differ from that of combination therapy with UPA and MTX, attract attention. The advantages of UPA include higher efficacy compared with ADA (SELECT-COMPARE) and ABC (SELECT-CHOICE) and the opportunity to overcome resistance to one or more bDMARDs (SELECT-BYOND). All this taken together expands the possibilities of pharmacotherapy for the most severely ill patients suffering from RA [78].

With regard to the prospects for a wider use of UPA in RA, the possibility of optimizing (reducing) the dose of UPA in patients who have achieved remission of the disease, as previously shown in patients treated with BARI, deserves a special study [79].

The effectiveness of UPA in RA is theoretically well substantiated. In the SELECT-NEXT and SELECT-BEYOND studies, it was shown that a decrease in RA activity (DAS28-ESR) during UPA treatment (12 weeks) was associated with normalized serum concentrations of key immunological biomarkers associated with RA immunopathogenesis [80]. These include IL6, IL1, IL12, IL15, IL18, IFNγ, IFNα, IFNβ, TNF, granulocyte macrophage colony-stimulating factor (GM-CSF), chemokines (CCL23, CCL7), matrix metalloproteinase (MMP) 3, S100A12 (S100 calcium-binding protein A12), which reflect the activation of macrophages, myeloid cells, and lymphocytes [81]. The pronounced anti-inflammatory and immunomodulatory effects of UPA were confirmed by a gene expression analysis (over 100 mRNA transcripts) in whole blood samples (Affymetrix Clarion S HT microarray) obtained from patients included in the SELECT-NEXT RCT [82]. This study demonstrated inhibited expression of the genes of a wide range of cytokines (IFNA, IFNB, IFNG, IL2, IL5, IL6, IL7, IL15, IL21, CSF-2, OSM, TGFB, TNFA), molecules involved in intracellular signaling (STAT, JAK, SYK, PI3K, PRKCA) and activation of the signaling pathway associated with Toll-like receptors (TLR2, TLR3, TLR4, TLR9), as well as other "pro-inflammatory" pathways involved in the activation of innate and acquired immunity, migration of leukocytes, and phagocytic activity. Important data were obtained in a comparison of the molecular effects of UPA and ADA (SELECT-COMPARE) using proteomic analysis (Olink platform) [83]. It was demonstrated that treatment with UPA and ADA leads to a decrease in the concentration of protein biomarkers associated with the functional activity of neutrophils/macrophages, but UPA had a better effect on the "immune" proteins involved in T-cell immune response, while ADA had a higher effect on M1 ("inflammatory") macrophages. The clinical effect correlated with a decrease in IL6, TNFRSF1A, MMP10, IL2RA, PLAUR, CCL2, TNFRSF10C, SERPINE1 in patients treated with ADA and with decreases in IL17A, IL17C, CCL11, CCL20, TIMP4 in UPA-treated patients. It is noteworthy that of the 184 proteins studied, none was associated with the clinical effects of both drugs. In general, treatment with UPA was accompanied by inhibition of a wider range of "pro-inflammatory" mediators compared with ADA therapy, which is consistent with the

SELECT-COMPARE study indicating a higher clinical efficacy of UPA compared with ADA.

In conclusion, it should be emphasized that, despite the strong theoretical basis and the convincing results of RCTs and long-term LTE studies showing the high efficacy and safety of UPA, the true place of this drug in the treatment of RA will be established during its use in real-world clinical practice in comparison with other JAK inhibitors and bDMARDs in the framework of international and national registries.

Transparency of the study

The study was not sponsored. The authors are solely responsible for submitting the final version of the manuscript to print.

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