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Gout and Rheumatoid Arthritis: Available Options for Pharmacotherapy. Overview of World Data

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Abstract

Due to adverse effects, old-age uricosuric medications have been withdrawn only to assisted treatment of gout. Their place was taken by Xanthine Oxidase (XOI) inhibitors as the first-choice medication. Although they are easier to monitor and free from many side effects, they have a limited spectrum of associations. New-generation uricosuric medications have been included in combination therapy with XOI. They can also be used alone in the case of patients with XOI intolerance. The latest studies seek to demonstrate the effectiveness of combination medications instead of selective medication class assessments. The aim of this part of the article is to review the global standards of pharmacotherapy for gout, with particular emphasis on recently promoted combination therapy. Combination therapy reduces the risk of side effects with comparable results to XOI or new generation uricosuric medications, sometimes even exceeding their effect.

Rheumatoid Arthritis (RA) is one of the most common autoimmune diseases of the skeletal system. Pharmacotherapy has evolved from non-specific anti-inflammatory medications to increasingly advanced biological agents. The latest activities involve the development of further bio-similar substitutes for known biological preparations. This part of the article analyzes the latest global achievements in the field of biological and bio-similar medications. Biologic medications offer even more than 60% effectiveness, which, however, falls dramatically in patients who do not respond to csDMARDs. Full effectiveness of pharmacotherapy requires a detailed understanding of the immune-pathological mechanisms of RA. It is recommended that pharmacotherapy is suited to the molecular classification.

Keywords: Pharmacotherapy of gout; Biological pharmacotherapy; Nonsteroidal anti-inflammatory drugs; Pharmacotherapy of rheumatoid arthritis; Xanthine oxidase

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Introduction

Due to adverse effects, old-age uricosuric medications have been withdrawn only to assisted treatment of gout. Their place was taken by Xanthine Oxidase (XOI) inhibitors as the first-choice medication. Although they are easier to monitor and free from many side effects, they have a limited spectrum of associations within their own medication group and must be used with caution especially in older patients. New-generation uricosuric medications have been included in combination therapy with XOI. They can also be used alone in the case of patients with XOI intolerance. The latest randomized studies seek to demonstrate the effectiveness of combination medications instead of selective medication class assessments. The progress of gout pharmacotherapy also involves the study of Il-1 blockers. Although their beneficial effects in the gout exacerbation phase have been confirmed, wider use is suppressed by numerous contraindications. Therefore, IL-1 blockers have been omitted in the previous recommendations of the National Institute for Health and Care Excellence. The aim of this part of the article is to review the global standards of pharmacotherapy for gout, with particular emphasis on recently promoted combination therapy.

Rheumatoid Arthritis (RA) is one of the most common autoimmune diseases of the skeletal system. Pharmacotherapy has evolved from non-specific anti-inflammatory medications to increasingly advanced biological agents. The latest activities involve the development of further bio-similar substitutes for known biological preparations. Despite the relatively good knowledge of the mechanisms of disease progression, precise knowledge about immune-pathogenesis is still missing, which reduces the effectiveness of treatment. Only an insight into molecular mechanisms will allow the final progress towards selective functionally targeted medications.

The part of the article about RA focuses mainly on the immunological basis of the disease. In the most comprehensive fragment, it is a review of the latest global research on the inflammatory response. In the paragraphs on pharmacology, in addition to the reminder of classic medications, it analyzes the latest global achievements in the field of biological and bio-similar medications, including those awaiting registration.

Gout

Pathophysiology and epidemiology

Gout involves painful arthritis, most often of the first metatarsophalangeal joint, resulting from the precipitation of monosodium urate crystals in the space of a joint and surrounding tissue as a result of hyperuricaemia [1]. After osteoarthritis (27 million cases), it is the most common type of arthritis in the adult US population [2]. In developed countries, especially in the USA and the United Kingdom, it reaches an incidence of 13.9/1,000 up to even 39/1,000, which increases with age [2,3]. Risk factors are also concomitant systemic diseases, such as heart failure, including congestive heart failure, atherosclerosis and Chronic Kidney Disease (CKD), as well as dietary errors with the following metabolic syndrome (type 2 diabetes, hypertriglyceridaemia, HDL lowering, hypertension, obesity) [3,4]. Cardiovascular episodes do not cause gout, but they coexist with it [4,5]. Studies conducted by Zhu et al., distinguish factors of obesity and hypertension, emphasizing their special impact on the increase in incidence in 1987-2007. It is worth noting that the conclusions came from surveys on a representative sample of Americans (N=5,707), whereas extrapolation of the trend was based on a comparison to a 3.29-fold larger sample from the previous study (N=18,825) [2]. Estimation made by Lawrence et al., indicates an increase in incidence from 2.1 million in 1995 to 3 million in 2005. At the same time, due to the lack of complete research, according to the authors, the full number of cases remains unknown [1]. Studies conducted by Soriano et al., apart from risk factors already listed-mentioned risk factors, such as excessive alcohol consumption, use of diuretics or cyclosporine, and among concomitant diseases-psoriasis [3]. Khana et al., supplement the list of diseases with myelo- and lymphoproliferative diseases. They also specify that risk factors may be both congenital (purine metabolism abnormality) and acquired (lead poisoning) [6]. The gender ratio among newly diagnosed patients is 4.42(m):1.32(f). The conclusions were based on 24,768 uncovered cases in the cohort of 1,775,505 of Britons aged 20-89 for the years 2000-2007 [3]. This value is probably underestimated, as studies conducted by Richette et al., show that only less than half the cases of gout are diagnosed [5]. In at least 90% of cases, gout results from hyperuricaemia caused by reduced uric acid excretion [7]. Physiologically, about 90% of the kidney-filtered urate is resorbed in the proximal tubule, and the remaining part together with 60-70% of uric acid is eliminated daily in the urine [8-11]. The coexistence of glomerular filtration anomalies with an increased mechanism of reabsorption leads to the retention of uric acid. Predictors of pathological enhancement of reabsorption are also: hypertension, insulin resistance, thiazide or loop diuretics and alcohol [12]. Excess fructose, especially in western diets, promotes hyperuricaemia [13], which involves the over expression of genes encoding URAT1 uric acid transporter, GLUT9 glucose and ABCG2 multi-medication resistance protein, SLC22A12, SLC2A9, ABCG2, respectively [8,14-16].

Purpose of pharmacotherapy and used medications

The purpose of pharmacotherapy for gout is to reduce the incidence of acute or recurrent seizures of pain and inflammation by lowering or maintaining serum urate below about 6.8 mg/dL (360 mmol/l) defining the limit of their solubility in urine [17]. In the phase of exacerbations, pharmacotherapy is based on NSAIDs and intra-articular corticosteroids. The chronic phase is treated with either allopurinol or febuxostat with/without probenecid. Benzbromarone and pegloticase [5,17-20] are also used to treat resistant forms. Despite the varied treatment methods, the results are often unsatisfactory. Patients who fail to normalize serum uric acid levels are prone to gout attacks. The latest studies on urate conveyors in proximal tubules enabled the development of new generation uricosuric medications, including lesinurad [14]. These medications are recommended for patients with both acute gout and resistant to allopurinol or febuxostat [5,18].

Types of pharmacotherapy

The history of gout pharmacotherapy began with acetylsalicylic acid. However, it was quickly eliminated due to adverse effects observed especially at high doses [17]. An increase in the incidence of gout especially in developed countries has motivated researchers to seek new pharmacotherapy methods. The solution was innovative medications that reduce urine concentration. To maximize the effect, synergistic agents were preferred to older generations of uricosuric medications [18]. The gold standard was XOI (Xanthine Oxidase Inhibitors), the advantage of which consisted in the lack of constant monitoring of urea concentration and the elimination of the risk of nickel alkylation during irrigation [18,19]. Uricosuric medications have been left for assisted treatment, especially in patients who are resistant to XOI, although their equivalence is still being discussed. Studies prove the comparability of effects with XOI, but with a significantly higher risk of nephrolithiasis and slightly increased hepatotoxicity [19-21]. Current randomized studies tend to be aimed at assessing the effectiveness of combination therapies rather than using uricosuric medications themselves, including even newer ones. There is evidence of higher effectiveness of combined treatment in the absence of side effects for the lesinurad-allopurinol combination and activities limited only to skin lesions for the lesinurad-febuxostat combination [22,23]. It was also shown that in combination with XOI lesinurad at a dose of 200 mg daily reduces the concentration of urea in the serum by 10-20%. It is recommended in combination with XOI and with GFR>45 ml/min [24]. In comparison to it, probenecid obtained comparable results, although with a smaller spectrum of applications (with the exception of 4-5 CKD stage). It is therefore only permitted in combination with XOI and with caution as a number of side effects have been reported [5,18,20]. Febuxostat, which in comparative studies showed even higher effectiveness than allopurinol, at a daily dose of 240 mg must be used with caution. However, side effects are less frequent and less serious than in the case of probenecid [25]. Taken together, allopurinol is considered to be the gold standard in the initial daily dose of 50-100 mg depending on the kidney response increased up to 900 mg daily after 4 weeks from the start of treatment, and in patients with intolerance or reduced metabolism of allopurinol, febuxostat at the initial daily dose of 80 mg and a maximum of 120 mg (the same period to increase the dose) [18]. In the event of failure, either sulfinpyrazone, benzbromarone or probenecid are added, or they are used separately [20,26]. In the phase of exacerbation, maximum doses of NSAIDs (selective COX-2 inhibitors) or 500 mg of colchicine in divided or single dose are

recommended [16,17,27]. For patients with intolerance to NSAIDs/colchicine, either prednisolone is recommended in an oral daily dose of 30-35 mg (or equivalent in intramuscular/intravenous/intra-articular injections) or IL-1 inhibitors (the second option is yet to be approved by the National Institute for Health and Care Excellence) [5,19]. The chances of more and more modern pharmacotherapy result in the progress in the precise determination of serum urea levels using URAT1 and GLUT9 markers encoded by SLC22A12 and SLC2A9 genes, as well as the ABCG2 marker. The direction of changes is to look for agents that guarantee low serum uric acid concentration while preventing relapse [8,14-16]. This postulate is trying to be implemented in several ways. Despite the association of gout markers with the reduction of uric acid excretion, one of the methods tested is the inhibition of URAT1 at least in some patients. However, the effects are varied [7,14]. A new anti-inflammatory component (e.g., arhalofenate) is also added to new selective URAT1 inhibitors [28]. In-depth molecular research allowed to determine the targets of URAT1 inhibitors: serine-35, phenylalanine-365 and isoleucine-481 [16]. Deepening knowledge is certainly conducive to the search for new generations of uricosuric medications capable of enhancing the XOI effect. A condition for success is, however, an increase in safety of therapy, especially in patients at the 3rd and higher stage of CKD [23,24,29].

The effectiveness of XOI-based therapy is limited because they cannot be combined arbitrarily. Studies have shown serious side effects for spectrum-broadening therapies (despite the spectacular therapeutic effect). Especially in older patients treated with XOI, there is an increased risk of renal failure [30]. An increase in complications is also noted for HLAB-genotype 5801 [30]. The success of XOI did not therefore hamper the research on the improvement of uricosuric medications, especially for patients with XOI intolerance, including patients with renal failure and women [30]. It has been proven that in a carefully selected group, adding losartan or fenofibrate to uricosuric medications can have a positive effect. Losartan decreases the serum uric acid level by 10% (fenofibrate by even more), although sporadic clinical trials decrease the reliability of the conclusions [20].

Mechanisms of action of medications

Uricosuric medications increase urine excretion through competitive inhibition of Organic Anion Transporters (OATs) responsible for reabsorption of filtered uric acid in the proximal tubule [31]. In addition to OAT (1,3 and 4), transporters are: URAT1 and GLUT9 [31]. Probenecid and benzbromaron are the main medications in the group. Sulfinpyrazone has very limited application [31]. The therapeutic effect is comparable to allopurinol, but with the risk of serious side effects: in the case of benzbromarone-serious hepatoxicity, probenecidosis-urolithiasis [7,8,21,22,32]. For comparison, neither probenecid nor allopurinol exhibit mitochondrial toxicity [31]. Also, in contrast to benzbromarone, they do not stimulate the Peroxisome Proliferator-Activated Receptor (PPAR-y) responsible for the increased cardiovascular risk (provided that the recommended doses are not exceeded) [7]. The superiority of allopurinol over probenecid is also due to the pharmacodynamic disadvantages of the latter, namely the inhibition of OAT1/SLC22A6 and OAT3/SLC22A8 causing medication-related interactions [33,34]. However, XOI intolerance or lack of therapeutic response continue to require the use probenecid. In the first case, it replaces allopurinol and in the second it is included in combination treatment [31]. Studies confirmed higher effectiveness of combination therapy than monotherapy [5,20,23].

In the proximal tubules, lesinurad acts as URAT1 and an OAT4 inhibitor. URAT1 is responsible for the absorption of uric acid, while OAT4 increases the hyperuricemia associated with the diuretic [7]. Lesinurad does not interact with OAT1, OAT3 or GLUT9 (as opposed to probenecid), but it has lower mitochondrial toxicity and a lower affinity for the Peroxisomal Proliferator-Activated Receptor (PPAR) [7] in comparison to benzbromarone. It is safe, but at a dose of 400 mg it may induce a reversible increase in serum creatinine concentration according to the majority of studies [35-37], with the exception of Tausche et al., who showed regression of the side effect in only less than half of the cases [38]. Therefore, combination with XOI is recommended [39].

Febuxostat (XOI) inhibits the transformation of hypoxanthine to xanthine and further to urate. Thus, it reduces the production of urate from purine precursors [40]. It should not be combined with azathioprine (or allopurinol). The combination may result in overproduction of the 6 thioguanine nucleotide and increase the risk of myelosupression [40]. However, there were no significant side effects of the combination of febuxostat with colchicine, naproxen, indomethacin, hydrochlorothiazide, warfarin or desipramine [41], whereas the combination with lesinurad (or arhalofenate) even increases the therapeutic effect [42,43]. In comparison to allopurinol, despite higher effectiveness, it is characterized by a slightly higher risk of cardiovascular events, including fatal ones. In the treatment of mild and moderate renal dysfunction, no dose adjustment is necessary [40]. However, one should always remember to monitor liver parameters, because febuxostat increases the activity of hepatic transaminases [40].

RA

Rheumatoid Arthritis (RA) is characterized by a chronic systemic autoimmune response against multiple joints (symmetrical) with an unknown etiology. Initially, it attacks small joints, then large ones. The disease is characterized by a high ability to progress. As a consequence, it quickly causes systemic complications, leads to deepening disability, is responsible for the risk of premature death and has serious social and economic costs. In etiopathogenesis attention is paid to synovial hyperplasia, the production of autoantibodies that damage the skin, blood vessels and muscles with subsequent osteoclastogenesis. The key role is played by cytokines and various groups of polypeptides, which are subject to advanced biological and clinical research. Among cytokines, IL-1a and b and TNF-alpha trigger the intracellular signaling cascade followed by the recruitment of innate and adaptive cells of the immune system, as well as the activation of mesenchymal factors and synoviocytes with induced agitation mediators, among others TNF-a, IL-1, 6 and 8. The effect is the formation of synovial inflammation, increased angiogenesis and lymphangiogenesis. The therapeutic challenge is to ensure a balance between pro- and anti-inflammatory cytokines (in the absence of precise knowledge about tolerance loss mechanisms). Although in literature, the view that only the final knowledge of etiology will guarantee satisfactory progress of pharmacotherapy is widely accepted, it is still unclear what specific synthetic and biological predictors are behind the disease [44-48]. RA is found in all regions and attacks all groups with 40/100,000 incidence increased by over-representation of the female gender. In addition, a higher risk, up to 6.3%, is found for two North American Indian tribes [49]. The corresponding risk values in gender cohorts are: women-1/28 (3%), men-1/59 (2%) [50,51]. However, the image of modifiable factors

is contradictory. Preventive action of contraception has been ruled out. Currently, its rather stimulating effect on the more severe forms of RA have been emphasized. The effects of hormone replacement therapy are also unclear [44,52].

The aim of RA pharmacotherapy is to reduce pain and inflammation, improve quality of life and optimize disturbed joint functions and prevent progression of the disease. Currently in pharmacotherapy for RA, the following are used:

1. Non-Steroidal Anti-Inflammatory medications (NSAIDs), e.g., diclofenac, naproxen.

2. Glucocorticoids (GKS), including prednisone, methylprednisolone.

3. csDMARDs disease modifying antirheumatic medications, among others methotrexate, leflunomide.

4. Targeted synthetic tsDMARDs, e.g., tofacitinib, baricitinib.

5. Biologic original boDMARDs, among others abatacept, certolizumab.

6. Bio-similar bsDMARDs), e.g., CT-P13, SB2 (bio-similar infliximab), GP2015, SB4 (bio-similar etanercept) [44,53-55].

Randomized placebo studies (N=3907) showed effectiveness of 53-78% of infliximab, cyclosporin, sulfasalazine, leflunomide, methotrexate, gold and auranofin compounds, glucocorticosteroids, anti-IL-1, the highest for infliximab before methotrexate and others, in the prevention of radiological progression. The same studies also suggested moderate effectiveness of D-penicillamine, hydrochloroquinone, pamidron acid, minocycline and chloroquine in the absence of cyclophosphamide effects. Only with the exception of anti-malaria medications, all the others were able to maintain the effects of treatment [56].

Immunopathology

The background to the pathophysiology of RA is the immune system's reactions within the two main subsystems: Pathogen-Associated Molecular Patterns (PAMPs) and Danger-Associated Molecular Patterns (DAMPs). The first ones are run by micro-organisms, the second ones are triggered by oxidative stress [57]. The imbalance of exo- and endogenous interactions on the body leads to auto-aggression [58]. Among autoimmune diseases, RA is the most common (next to autoimmune thyroiditis). Their etiopathogenesis is based on the production of autoantibodies and hyperreactivity of the system with subsequent self-fibrosis and response of T lymphocytes [46]. The current interest of immunologists is shifting towards the clonal deletion of autoantibodies, allowed by refutation of the assumption about the role of lymphocytes in the recognition of self-foreign antigens. It turned out that they behave equally independent of the origin of the antigen and only in the specific cytokine microenvironment [44,48,49].

In RA, the rheumatoid factor (IgG) and anti-CCP autoantibodies are responsible for auto-aggression. In addition to cytokines, the inflammatory environment is made up of chemokines. The clinical image, including complications, includes osteoclastogenesis and angiogenesis, ranging from synovial hyperplasia16. A detailed mechanism consists in the penetration of macrophages, plasma cells and autoimmune complexes through the synovium, where they combine into lymphoid masses with their own germinal centers. There is an increase in macrophage-like synoviocytes (normally synoviocytes come from the mesenchyma) and fibroblasts responsible for the production of inflammatory factors: cytokines, chemokines, adhesion molecules, metalloproteinases of the extracellular matrix (MMP-3, MMP-9 and MMP-13), angrecanases (disintegrin, thrombospondinase metalloproteinase-ADAMTS-4 and 5), as well as for the reduction of the Tissue Metalloproteinase Inhibitor (TIMP) level. This leads to digestion of the extracellular matrix with subsequent damage to joint structures [44,45,60].

Conventional, biological and bio-similar pharmacotherapy

The lack of precise knowledge about the causes makes treatment difficult. So far, the effectiveness of treatment results only from the recognition of the mechanisms of progression. On the other hand, therapies that are aggressively oriented towards clinical remission are preferred [45]. The treatment is based on NSAIDs and Glucocorticoids (GKS), disease-modifying medications (DMARDs), biological (included in therapy in 1998) and biosimilar [61-64].

The detailed list includes:

1. Ibuprofen, naproxen, ketoprofen, piroxicam, diclofenac, celecoxib – NSAIDs.

2. Methylprednisolone, prednisone, triamcinolone acetonide, triamcinolone hexacetonide – GKS.

3. Auranofin (oral gold preparation), sodium aurotiomalate (gold compound), azathioprine, cyclosporin, D-penicillamine, hydroxychloroquine, leflunomide, mycophenolic acid, sulfasalazine, cyclophosphamide-csDMARDs.

4. Tofacitinib (inhibitor of JAK1 and 3 kinases), fostamatinib (Syk kinase inhibitor), baricytinib (inhibitor of JAK1 and 2 kinases), apremilast (small molecule PDE4 inhibitor), imatinib (small molecule inhibitor of BCR-ABL1, C-KIT and PDGFR), ibrutinib (a small molecule BRT kinase inhibitor)-tsDMARDs.

5. Abatacept (T-cell costimulation inhibitor), adalimumab (anti-TNF-alpha), anakinra (anti-IL-1), certolizumab (anti-TNF-alpha); etanercept (anti-TNF-alpha), golimumab (anti-TNF-alpha), infliximab (anti-TNF-alpha), rituximab (anti-CD20), tocylizumab (anti-IL-6), ofatumumab (human monoclonal antibody) IgG1-in Poland only in the treatment of leukemia), atacicept (recombinant B-cell inhibitory protein), denosumab (human monoclonal antibody IgG2 against RANKL-in Poland, treatment of osteoporosis in postmenopausal women, bone complications in prostate cancer, bone prophylaxis in bone metastases of solid tumors), tofacitinb (JAK1 kinase inhibitor, 2 and 3 and weak TyK2 kinase inhibitor), fostamatinib (Syk kinase inhibitor-approved in the US), secukinumab (anti-IL-17a)-boDMARDs currently used.

6. Canakinumab (human IL-1b binding monoclonal antibody), Sirukumab (human monoclonal antibody binding IL-6) - boDMARDs in the testing phase.

7. CT-P13, SB2 (biosimilar infliximab), SB4, GP2015 (biosimilar etanercept), CT-P10 (biosimilar rituximab), BI695501 (biosimilar adalimumab-only the US), ABP501 (biosimilar adalimumab-the US and EU), SB5 (biosimilar adalimumab-only EU) - bsDMARDs currently used. In 2017, 25 medications in the group.

8. CHS-0214, HD203, LBEC0101 (biosimilar etanercept) - bsDMARDs in the testing phase/prior to registration [44, 53-55].

Methotrexate (csDMARD) is still the most widely used [65]. Due to the lack of knowledge about biomarkers of therapeutic response and toxicity, medications (including biological ones) have only limited effect, and the inability to achieve remission extends pharmacotherapy. Available disease classifications are based solely on the clinical image, although they should be based on a molecular classification with separate prognoses and treatment regimens [44,66,67].

New trends in pharmacotherapy focus on stimulating cellular and humoral responses. As for the former, the role of type 1 T lymphocytes has been previously stressed. Recently, attention has been drawn to Th17 responsible for the production of IL-17, IL-17F, IL-21, IL-22, and independently of them on TNF-alpha. The lack of fully reliable information about T lymphocytes (in large amounts accumulating in the synovial synovium) excludes the therapeutic use of cyclosporin [68]. It is certain, however, that treatment requires the use of agents with a very wide spectrum, including:

1. Monocytes, macrophages, neutrophils, basophils, eosinophils, erythrocytes, dendritic cells and megakaryocytes/platelets - myeloid cells producing IL-12, IL-15, IL-18, IL-6, IL-32-dendritic cells of plasmocytoids.

2. Type IIHLA molecules.

3. Molecules that activate and stimulate the presentation of T lymphocytes.

Medications that interrupt the interaction of CD28 with CD80/CD86 are recommended [69,70]. Another way is to affect TNF-alpha, regarding which the effect on the dysregulation of auto-controlled T-cell mechanisms was confirmed. Studies of mechanisms of humoral response in RA showed activity of APRIL (T-cell proliferation ligand), B-cell stimulator (BLyS), as well as CC and CXC chemokines [71]. In addition, the pathogenic role of CD 20+ of B lymphocytes has been demonstrated in rituximab therapy. It is based on the stimulation of interleukin-6, TNF alpha, lymphotoxin-b or TNF-c [72]. Comprehensive pharmacotherapy requires consideration of the pathway of neutrophil infiltration from the bone marrow to the synovium, including transport factors. Here, in turn, the role of macrophages-CSF, granulocytes-CSF and granulocyte-macrophages-CSF is emphasized [73]. Releasing TNF alfa, IL-1, IL-6, IL-12, IL-15, IL-18, IL-23, reactive oxygen and nitrogen, macrophages are responsible for inflammation. They are themselves activated by: TLR (2-4 and 8) and NOD (Nucleotide binding Oligomerization Domains, including immune complexes of lipoproteins, liver X receptor agonists and protease activated receptor 2). As for cytokines, microRNA-155 affinity was also demonstrated among macrophage activators [74]. The mast cells also have a similar role to neutrophils. Detailed targets confirm the participation of the immune system in the stimulation of inflammatory processes. This is also confirmed by the correlation between the increase in cytokines and chemokines and the degree of progression, ranging from IL-13,14,15 and indirect stimulation through T-lymphocytes and stromal cells, to expression of adhesion molecules, T-cell dysregulation, pain response and angiogenesis. TNF-alpha remains the leading cytokine [75-77]. In the pharmacotherapy of RA, blocking of IL-1a, IL-1β, IL-18 and IL-19 (family of interleukins 1) responsible for stimulation of leukocytes, endothelial cells, chondrocytes and osteoclasts has been proven. An equally effective method is the blockage of metabolic pathways: JAK, splenic tyrosine kinase, NF-kb and p38-activated mitogen protein kinase. Tafacitinib with this mechanism of action and fostamatinib with an inhibitory effect on splenic tyrosine kinase has proven effectiveness in clinical trials. With the exception of p38-activated protein kinase, all metabolic pathways have effective inhibitors [78]. The role of cytokines is not limited to causing an inflammatory response, but extends to osteoclastogenesis. However, other predictors also influence this process, including prolactin, corticosteroids, parathyroid hormone, peptide associated with parathyroid hormone. RANKL receptor blockage is competitive towards the cascade of stimulation of osteoclastogenesis [79,80]. Still, the decisive role is attributed to T lymphocytes.

Side effects of pharmacotherapy include fatal cardiovascular events, but the liability of glucocorticosteroids or NSAIDs has been ruled out [81]. Research shows the influence of inflammatory mediators involving the activation of vascular endothelial cells with subsequent instability of atherosclerotic plaques. In-depth studies have shown the involvement of hepatic reactants of inflammatory agents: C-reactive protein, mannose-binding protein, complement elements, ferritin, ceruloplasmin, as well as amyloid A, haptoglobin, serpin and alpha-2-macroglobulins (inhibitory agent). The same reagents, however, are responsible for fatal cardiovascular episodes in healthy people as well. In the group of long-term effects, insulin resistance of adipose tissue and muscles is mentioned [82]. Since the goal of treatment is non-selective prevention of antigens that may affect the tissue, patients experience a reduction in both HDL and LDL. Among medications used in RA, statins restore the lipid balance and, as a consequence, compensate for the effects of induced insulin resistance [83].

However, prednisolone increases mortality when not being able to inhibit the disease [84]. The highest effectiveness of DMARDs was recorded for the first 6 months [85]. DMARDs remain the gold standard of pharmacotherapy also due to minimal side effects [86]. The combination therapy using metrotoxate with sulfasalazine and hydroxychloroquine is the most effective [87]. In comparison to this, azathioprine, cyclophosphamide, cyclosporin or D-penicillamine results in the side effect of immunosuppression.

Mechanisms of action of medications

The mechanism of action of arylpropionic acid derivatives (ibuprofen, naproxen, ketoprofen) is based on the nonselective inhibition of COX leading to the transformation of arachidonic acid into Prostaglandins H2 (PGH2) to functionally diverse forms (mediators of pain, inflammation and fever). The interaction of n-aryl-substituted anthranilic acid derivatives (diclofenac) is a non-selective inhibition with anti-inflammatory, limited analgesic and antipyretic role. Diaryl-5-membered heterocycles (celecocib) show a selective inhibition mechanism (COX-2) [88]. The mechanism of glucocorticosteroids, thanks to the lipophilic structure, consists in penetration through the cytoplasmic membrane and easy activation of the cytoplasmic GCR receptor. The glucocorticosteroid-receptor complex then binds to the elements of the glucocorticoid response-GRE in the nuclear DNA leading to the expression of genes responsible for the production of anti-inflammatory proteins. This effect is complemented by the inhibition of genes encoding proinflammatory proteins [89]. Gold compounds inhibit b-glucuronidases, elastases, Thioredoxin Reductases (TrxR), and cathepsins B and C. Their interaction extends to inhibiting leukocyte infiltration, modulating neutrophil adhesion, and modifying macrophage activity. In addition, medication metabolites directly binding to T-cell receptors

block antigen signaling [90]. Auranofin inhibits the transcription of the NF-kb protein complex and thus reduces the secretion of inflammatory COX-2 enzymes [91]. Other factors of inflammatory response include: nitric oxide, TNF-α, IL-1b and IL-6. Azathioprine blocks the formation of amidophosphoryltransfer and indirectly purine synthesis in the process of T and B lymphocyte proliferation. In addition, it prevents full activation of already synthesized T lymphocytes, and in mature ones triggers apoptosis [92]. Leflunomide inhibits Dihydrogen Dehydrogenase of the mitochondrial enzyme (DHODH), and also forces the synthesis of *de novo* Uridine Monophosphate (rUMP), hindering the rapid multiplication of T lymphocytes [93]. Mycophenolic acid inhibits inosine-50 monophosphate dehydrogenase and reduces tetrahydrobiopterin. The result is a disruption in the synthesis of T and B lymphocytes, and by inhibiting their recruitment to inflammatory sites, it counteracts the inflammatory response. The direction of the anti-inflammatory effect is to reduce the irritating effect of metabolites [94]. Ciclosporin blocks calcineurin, and by binding to cyclophilin it blocks the release of cytokines (previously inhibiting dephosphorylation of the nuclear factor of active Th lymphocytes) [95]. Cyclophosphamide alkylates CD4, CD25 and Treg lymphocytes (factor-nitrogen mustard), eliminating them along with TNF 1 and other growth factors [96]. Methotrexate suppresses T and B lymphocytes and adhesion molecules. Inhibition includes Dihydrofolate Reductase (DHFR), methyltransferases, as well as enzymes involved in purine metabolism. In addition, it induces apoptosis of already-formed lymphocytes before increasing their sensitivity to CD95. Parallel anti-inflammatory action involves blockage of IL-154. Sulfasalazine exerts a damping effect on NF-kb by blocking IkB a and b kinases. Its metabolite, sulfapyridine, also has an antiarthritic effect [98]. D-penicillamine reduces the number of T lymphocytes, inhibits IL-1 production and disturbs the function of macrophages [99]. Hydroxychloroquine alkalizes lysosomes (Ph 4 to Ph 6) leading to reduced chemotaxis, phagocytosis and superoxide production by neutrophils. In addition, it inhibits the products of the non-specific inflammatory response (neurotransmitters for TLRs) [100].

Biological medications

boDMARDs were introduced in 1998. They arrest the progression of the disease even in 63.8% of cases [101]. Inclusion criteria are high OB or CRP, however, the condition for continuing treatment is a reduction of at least 20%, while reducing the number of inflamed joints by at least half [102]. boDMARDs, usually anti-cancer factor of necrosis (anti-TNF-alpha), are associated with one of csDMARDs (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine) [101]. Ineffectiveness forces the replacement with a combination therapy with another anti-TNF-alpha, preferably with a different target, with rituximab or with one of the JAK kinase antagonists (tofacitinib, baritinib). Recent clinical trials confirm the validity of this model as the option of choice in the second and third-line treatment [65]. Trials also showed correlations between the serological profile and the effectiveness of selected pharmacotherapy regimens. It also turned out that serologic diseases do not reduce the effectiveness of anti-TNF-alpha, and HIV does not lower the effectiveness of abatacept, tocilizumab or rituximab. However, contraindications to anti-TNF-alpha include: tuberculosis, multiple sclerosis, cancers and heart failure [103].

The safety of therapy requires constant control of immunosuppressive factors. The risk of infection in RA is 3-6%. One should strive to reduce the dose of glucorticosteroids or choose the safest biological medications possible (abatacept, rituximab, etanercept) [104]. A pre-requisite for the anti-TNF-alpha implementation is a screening test for tuberculosis, hepatitis B and C and HIV. For IL-6 blockers, hematology tests are required before inclusion. The continuation of abatacept or rutixxab treatment is dependent on monitoring of CD19 and immunoglobulin levels. Regardless, routine flu, pneumonia and shingles vaccinations are recommended for all patients [105].

Conclusions

The evolution of gout pharmacotherapy has, above all, sought to reduce the side effects observed for the first uricosuric medications. The priority was to increase the safety of treatment.

Combination therapy reduces the risk of side effects (or eliminates them completely) with comparable results to XOI or new generation uricosuric medications, sometimes even exceeding their effect.

Full effectiveness of pharmacotherapy requires a detailed understanding of the immunopathological mechanisms of RA. Until now, only the mechanisms of progression have been well recognized, and the treatment regimens are based on the clinical image. However, it is recommended that pharmacotherapy is suited to the molecular classification.

Biologic medications offer even more than 60% effectiveness, which, however, falls dramatically in patients who do not respond to csDMARDs. It is recommended to carefully select patients, second- and third-line treatment regimens, as well as to quickly eliminate the therapy in case of definitive ineffectiveness.

In 2017 there were 25 medications from the boDMARDs group on the European market. The introduction of bsDMARDS was regulated by the world's first legislation on bio-similar medications.

Previous meta-analyzes from clinical trials have demonstrated comparable effectiveness and safety of bio-similar boDMARDs replacements. The trials did not show any more side effects of bsDMARDS either during or after the therapy.

Author Contributions

D.W. and I.U. designed the study. D.W. surveyed the literature. D.W. and I.U. analyzed the information. D.W. wrote the manuscript.

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