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Perioperative management of patients with rheumatoid arthritis

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Abstract. Patients with rheumatoid arthritis (RA), despite the success of conservative therapy, have an urgent need for the orthopedic surgical interventions, as well as operations for somatic indications. These patients need a careful perioperative assessment and instruction for the favorable results of surgical treatment and management to be achieved in the postoperative period. A detailed history should be compiled, a thorough physical examination with appropriate laboratory evaluation of the organic and systemic functions, differentiation of the organic damage secondary to the RA or associated with comorbidity, should be carried out. Patients should be informed about the potential risks of surgery, including an increased risk of infection, delayed wound healing and development of venous thromboembolism events, as well as the key possibilities in terms of cardiovascular, pulmonary and neurological disorders that may be caused by surgery. Clinical studies over the past few years have improved our understanding of the proper perioperative management of patients with the RA. This article summarizes the latest advances in this field and considers the latest recommendations proposed by the American College of Rheumatology and the American Association of Hip and Knee Surgeons guidelines (2017) for the perioperative management of antirheumatic therapy in patients with rheumatic diseases undergoing elective total hip or total knee arthroplasty, and The British Society for Rheumatology guidelines on the disease-modifying antirheumatic drugs (DMARD) safety in inflammatory arthritis. The management of DMARDs in the preoperative period should be carried out under the recommendations of the leading rheumatological societies, but the approach should be individualized with the involvement of a multidisciplinary team. Today, the recommendations support the continuation of synthetic DMARDs throughout the entire perioperative period and recommend a short-term interruption of biological therapy at one dosing interval before surgery with a continuation of administration within 14 days after surgery. The higher doses of glucocorticoids contribute to the risk of postoperative infection more significantly than the biological therapy. It is recommended to avoid the planned surgery if the patients are receiving prednisone at a dose of more than 20 mg per day. Before surgery, it is recommended to reduce the dose of glucocorticoids to the lowest possible level. Even though uncertainty remains, these recent studies and recommendations allow a more rational and scientifically sound approach to the management of RA patients who are scheduled for surgery or who need to get operated urgently.

Keywords: perioperative management; rheumatoid arthritis; joint replacement; infection, risk; disease modifying antirheumatic drugs; glucocorticoids; biological therapy; tumor necrosis factor inhibitors

Despite the rapid development of biological therapy and decisive establishment of such medication in the rheumatic disease management, rheumatoid arthritis (RA) patients are often subjected to orthopedic surgical interventions [1]. Joint endoprosthetics, arthroplasty, arthroscopic debridement, tendon reconstruction, rheumatoid nodule removal, tunnel and wrist canal decompression – all of these proce-

dures, and numerous others, make up a list of orthopedic interventions indicated to treat rheumatoid arthritis. Furthermore, the RA patients undergo surgery due to their somatic conditions much more often than the rest of the population [1]. Perioperative period involves a number of infection-related risks, such as surgical wound infection and pneumonia. Arthroplasty and other interventions involving prosthet-

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ics cause a serious concern due to the possible risk of endoprosthetic devices becoming infected. One of the urgent issues and challenges the clinicians are facing is determining the scale of required examinations, frequency of monitoring sessions and required corrections to the therapy of RA patients either preparing for or already subjected to the surgical interventions.

A careful pre-operative assessment of the RA patients is undoubtedly essential despite the remission or pharmacological control of clinical symptoms. Very often the RA patients are subjected to the urgent surgical interventions, even at the peak of inflammatory autoimmune process. Taking into account the fact that the RA patients are considered a high risk group, the regulating societies in charge of rheumatologic condition treatment consider perioperative management of such patients to be an interdisciplinary issue, requiring involvement of a rheumatologist, anesthesiologist, cardiologist, hematologist and operating surgeon/orthopedist [2].

We are presenting our analysis and summarized review of international guidelines on the pharmacological RA treatment in the perioperative period. Its principal effort is centered on minimizing iatrogenic and postoperative risks.

The recent studies, including the amended guidelines, expanded our understanding of the infection risks in the RA, namely in those patients subjected to surgery, and the role of immunosuppressants, glucocorticoids (GCs) and biological therapy. Despite the remaining uncertainty and lack of consensus on certain points of the guidelines, they incite a more rational and evidence-based approach to the RA treatment of patients who are to undergo the planned or urgent surgery.

Recommendation on the preoperative period

Anamnesis and objective examination

In case of a planned surgical intervention, there should be performed a comprehensive assessment of all complaints, performed a detailed analysis of anamnesis and physical examination. The details of personal and medical history, such as age, duration of illness, functional condition, specific articular lesions, extra-articular signs, may determine the necessity of additional examinations. Information on the pharmacological history, duration and GC use, complications following the previous interventions and comorbidities should be gathered. Among the comorbidities that should be taken into account and possibly ruled out by laboratory and instrumental means of examination there are anemia, Felty syndrome (FS), interstitial pulmonary disease, pleurisy, neuropathia, vascular diseases, ischemic heart disease, pericardi-

tis, uveitis/scleritis, Sjgren syndrome (SjS), cervical spine disorder, and cricoarytenoid arthritis [3]. In addition to the regular preoperative objective examination, attention is focused on the patient's posture, gait, articular mobility and epidermal integrity.

Preoperative testing

The regular preoperative testing is required in order to find out the extent of the disease's progression, especially if the RA patients have long been taking the disease-modifying anti-rheumatic drugs (DMARDs), non-steroid anti-inflammatory drugs (NSAIDs) and GCs.

It should be noted that the RA patients often have anemia both as a result of principal condition and as a side effect of medication, and leukopenia; both conditions are diagnosed by means of a complete blood count [3]. Biochemical blood test with obligatory hepatorenal analyses is also required, especially if there are hepatorenal disorders, secondary as to the principal condition and, very often, a product of antirheumatic medication. Other routine postoperative studies include urine tests, bacterial urine culture, electrocardiography, X-ray of chest organs. Postoperative assessment of other comorbidities is necessary for reducing complications following surgical diseases and mortality [4].

Comorbidities

Assessment and screening for the RA-associated cervical spine diseases, cardiac, pulmonary and neurological conditions may help diminish the risk of adverse postoperative complications.

Cervical spine

Atlantoaxial instability

The prevalence of cervical spine disorders in the RA patients varies from 25 to 86 % and is associated with a spinal cord damage risk during the intubation [5]. In the preoperative period, it is vitally important to rule out the cervical spine disorders, as well as to evaluate the extent of (non-)involvement for the nervous system. This requirement is attributed to the fact that up to 80% of the RA patients have the X-ray signs of cervical spine disorder even though half of them do not manifest any clinical signs [5]. Furthermore, 36 % of patients with characteristic symptoms develop a rapidly progressing neurological disorder [6].

The neurologist or anesthesiologist should perform a complete neurological examination of these patients in order to understand the clinical implications of cervical spine's neurological involvement and, more importantly, to determine the neurological baseline to be compared against the further postoperative changes.

There are three most prominent RA-related cervical spine deformations: atlantoaxial subluxation (65 %), vertical shift of odontoid process (20 %) and subaxial subluxation (15 %) [5]. There should be a preoperative assessment of atlantoaxial subluxation performed to rule out the cervical hypermobility. A higher incidence of atlantoaxial subluxation was revealed in patients with a longer anamnesis, peripheral articular erosions, long-term GC therapy and subcutaneous nodules [6]. Vertical shift of odontoid process and atlantoaxial subluxation occur secondary to the inion erosion and articular changes at the level of C_1 - C_2 . The above mentioned disorders result in a brain stem's direct compression by the odontoid process, leading to the severe neurological damage and even death. Subaxial instability and vertebral subluxations in C_2 - C_7 segments are mostly associated with thoracic kyphosis [5].

Regular static X-rays of cervical spine, along with dynamic lateral X-ray assessments of flexion and extension capacities should be performed prior to surgery in those patients with pre-disposing factors, in order to test the instability of C_1 - C_2 . They are also necessary in case of cervical pain, limited cervical mobility, root syndrome, pain and weakness of limbs [6].

Anterior atlantodental interval (AADI), i.e. distance from the posterior edge of C_1 curve to the anterior surface of odontoid process, is the most widely used parameter to measure these anomalies. Its normal values are less than 3 mm. In case of instability, this parameter will increase with flexion, which may be seen at the lateral X-ray image. Although the AADI is a non-specific tool for neurological deficit diagnostics, the AADI-based examination is necessary to decide upon further therapy in order to prevent the atlantoaxial instability in the RA patients during the perioperative period.

If the AADI parameter is over 2.5 mm, anesthesiologist should be informed about this fact, especially in the pre- and perioperative periods. Patients with atlantoaxial instability need to be monitored for any new neurological symptoms of progressive deformation, which, untreated, may result in the atlas' destruction. It leads to a brain stem compression, and the perioperative patient's predisposition to the neurological damage. In case of present neurological symptoms, the RA patient should undergo the cervical MRI in order to evaluate the extent of spinal cord compression [5]. If the compression is diagnosed in the perioperative period, additional safety measures, i.e. soft collar, minimal manipulations while being transported around etc., may be necessary [5].

Cricoarytenoid arthritis

Cricoarytenoid arthritis is widely spread among the RA patients (26-86%) [6]. RA is the only systemic au-

toimmune disease involving joints and laryngeal cartilages into its pathological process. Despite the high prevalence of cricoarytenoid arthritis, acute airways obstruction remains a fairly rare though dangerous complication. In case of bilateral cricoarytenoid arthritis, patients often experience suffocation, while in a paramedical position, and require an urgent tracheotomy. The RA patients complaining of a 'lump' in their throats or strain, hoarseness, odynophagia or pain while speaking should be examined for cricoarytenoid arthritis in the preoperative period. Pain irradiating into the ears due to the cricoarytenoid joint strangulating the glossopharyngeal and vagus nerves is also a frequent complaint. Chronic cricoarytenoid arthritis is usually symptomless or misdiagnosed as a chronic bronchitis or asthma. Attended by the RA in the perioperative period, the cricoarytenoid arthritis may result in an acute breathing failure during ex/intubation, requiring such urgent measures as tracheotomy [6].

Cardiovascular system assessment

Assessment of cardiovascular disease (CVD) risk is an obligatory task of a surgeon or anesthesiologist in the pre/perioperative periods. The Patients suffering from the RA or other inflammatory articular diseases have a significantly elevated CVD-related mortality risk, almost 50 % higher than the rest of population [7]. This fact accounts for the importance of their management in the preoperative period.

Existing correlation between the RA activity and higher CVD risk is demonstrated by a range of studies: there is a relative increase of not only cardiovascular risks, but also early mortality due to other causes, compared to the healthy controls [9]. Another study reveals an elevated angina and myocardial infarction (MI) (both undiagnosed and resulting in a hospitalization) risk in the RA patients compared to the non-RA patients [10]. It should be mentioned that, according to the recent findings, patients with a low RA activity and no CVD history also had a high mortality risk, related to the cardiovascular causes [11]. All the above mentioned facts emphasize the importance of early CVD diagnostics and treatment in the RA patients, especially with pending surgery.

To evaluate the cardiovascular risks of the RA patients in the preoperative period, three essential diagnostic procedures are required.

(1) Electrocardiogram (ECG or EKG) is a vital diagnostic tool, required pending surgery in the RA patient in order to evaluate the present arrhythmias and QT interval. The RA patients are especially susceptible to the QT interval extension, which is an adverse sign of arrhythmias and sudden cardiac death [11].

(2) Although systemic assessment of coronary risk by the SCORE scale to foretell a 10-year CVD risk

is not required from the orthopedic surgeon, it is a useful prognostication tool, which may help managing the preoperative patients [12]. The SCORE scale data for the RA patients should be multiplied by 1.5 in order to take into account a 50 % RA –related risk elevation, compared to the rest of population [12]. For the cardiovascular risk assessment the interdisciplinary medical team may recruit a cardiologist.

(3) Assessment of the inflammatory process' activeness in the RA patient is an essential factor of the progressing disease. The key RA and elevated inflammation marker–related dysfunction is the thickening of carotid intima–media. Although the clinical value of this index is less noticeable, it is essential to recognize its association with a set of RA risk factors [12]. Ultrasound examination of cervical vessels helps calculating the carotid intima media thickness (CIMT).

Peripheral vessel diseases also constitute a potential risk of postoperative complications in the RA patients. This fact may be explained by two reasons. First and foremost, the RA patients have an elevated risk of such comorbidities, as vasculitis, vasospasm and Raynaud's disease. It is thus recommended to avoid ice applications in the postoperative period. Secondly, if a surgery were performed to correct minor articular hand and feet deformations, postoperative recovery might take longer time and require vascular lesion monitoring in order to prevent ischemia [13]. In case of the preceding severe and long-standing deformations this monitoring is especially needed.

The RA is a complex and multifactorial disease, affecting numerous systems and organs, namely cardiovascular ones. Although an orthopedic surgeon is not supposed to treat CVDs, he/she should be able to recognize this comorbidity in the RA patients, as only a comprehensive perception of the RA patient's status allows effective integration of an orthopedic surgeon into a multidisciplinary treating team.

Respiratory damage assessment

The RA is associated with several pulmonary diseases, including an interstitial lung disease (ILD) and medication-induced diseases, secondary to the long-term DMARD use. According to one theory, pulmonary damage in the RA patients is associated with the produced antibodies against cyclic citrullinated peptides (CCPs). Citrullinated proteins are produced as a result of post-translational modification of arginine in a peptidyl-arginine deaminase-catalyzed enzymic reaction. The above mentioned enzyme of synovial fluid catalyzes arginine's transformation into citrulline in case of the present inflammation. With the RA, peptidyl-arginine deaminase causes a localized citrullination of synovial sheath proteins, i.e. a principal autoantibody trigger. Vimentin, filag-

grin and fibronectin are synovial proteins than may get citrullinated, as a result producing the antibodies presumably also bearing connection to the pulmonary diseases attending the RA [14]. Citrullination is considered a marker of connective tissue inflammation, associated with other inflammatory conditions, such as idiopathic pulmonary fibrosis and multiple sclerosis (MS) [14]. The well-known RA-attending pulmonary disease risk factors are older age, male sex, history of smoking or smoking at present, as well as a long-term methotrexate use. There is a recent hypothesis that anti-cyclic citrullinated peptide (CCP) antibodies predict the RA-related extra-articular features, namely pulmonary damage [14, 15].

RA-associated interstitial lung disease

The most frequently diagnosed RA-associated pulmonary damage is an interstitial lung disease (RA-ILD). The RA-ILD most often manifests itself by an idiopathic interstitial pneumonia, complicating the differential diagnostics. Among other clinical manifestations there may be acute eosinophilic pneumonia, apical fibrobullous disease, rheumatoid nodules and amyloidosis. Acute respiratory symptoms in the RA patients during the perioperative period should become a warning, requiring a further diagnostics, such as a chest X-ray and CT [15]. Very often there is incongruence between the symptomless/low-symptomatic pulmonary disease and instrumental data. That is why clinical observations should be compared with instrumental findings for an early detection and appropriate treatment of the RA-attending pulmonary damage.

Medication-induced pulmonary diseases

DMARDs are the key therapeutic options for the RA; however, they're capable of inducing iatrogenic pulmonary damage/disease. Pneumonias, upper airway diseases and pulmonary nodules constitute well-known side effects of the DMARD use [14, 15]. Other serious side effects, typical of biological DMARDs, result from their pulmonary toxicity, provoking mortality in 35.5 % of cases [16]. Toxic pulmonary damage is registered most often with methotrexate, aurum salts, sulfasalazine (SSZ) and penicillamine. Pulmonary damage is also possible due to such biological drugs, as tumor necrosis factor (TNF) inhibitors, increasing tuberculosis and other opportunistic infection risk.

Methotrexate-induced pulmonary pathology has the following risk factors in the RA patients: older age, diabetes, pleuropulmonary rheumatoid changes, past DMARD use, hypoalbuminemia. A special study prompted the conclusion that the preceding changes, i.e. interstitial infiltrates, seen at the X-ray images,

predispose the subject to the methotrexate (MTX)-induced pneumonitis. The researchers suggested a range of criteria distinguishing the MTX-induced pneumonitis from the RA-ILD: 1) methotrexate use for no less than 4 weeks prior to the pulmonary damage symptoms' occurrence (obligatory criterion); 2) other pulmonary diseases (including infectious ones) ruled out; 3) recurring or modified infiltrates at the repeat chest X-rays; 4) clinical course typical of the hypersensitivity reactions; 5) pulmonary morphological picture typical of the drug-induced pathology.

With the RA, pulmonary damage may be provoked by the disease itself, infection and use of the modern basic anti-inflammatory drugs. In the preoperative period, a careful anamnesis collection, pulmonary damage risk assessment at present, spirometry, lung X-ray and/or CT are essential.

Neurological complications

The RA patients may have various nervous disorders, secondary to the principal complaint. Compression and peripheral neuropathies are especially common, with the latter possibly drug-induced. Their assessment should be performed pending the surgery in order to ascertain whether additional interventions are necessary, namely tarsal tunnel release prior to the lateral calcaneal osteotomy in case of an advanced distal neuropathy [13].

Venous thromboembolism (VTE)

Venous thromboembolism (VTE), especially the deep vein thrombosis (DVT) and pulmonary embolism (PE), is a possible complication of the RA in the pre/perioperative periods whose risk is rather high [17, 18]. In the RA-attending VTE risk meta-analysis, W. S. Chung et al. (2013) revealed that the RA-attending VTE incidence is 2.18 % than in the rest of population. However, the follow-up assessment 1 year after the surgery showed no elevated risk of VTE-related hospitalizations, allowing us to suggest that a standard VTE prevention is enough for the RA patients in the perioperative period.

Postoperative infection risk in the RA patients

A range of studies show that the RA patients have an elevated risk of postoperative infection due to the orthopedic interventions [19-22]. R. L. Cordtz et al. (2018) [20] recruited 3913 RA patients having undergone hip and knee replacements from the Danish register and found a higher infection risk for the replacements (odds ratio (OR) 1.46). A similar study with the national sample data for the in-patients revealed higher values for the postoperative infections, suture inconsistency, and long-term wound healing, system-

ic complications of the hip and knee replacements in comparison with osteoarthritis patients [21]. Extrapolating the data to other orthopedic interventions, J. A. Horowitz et al. (2018) [22] detected a higher percentage of postoperative infections in the RA patients after the femoral arthrodesis (2.6 % vs. 1.5 %). The primary reason of the RA-related postoperative infectious complications remains unclear: whether it is the medication, chronic systemic and local articular inflammation or various comorbidities.

Recommendations for the RA patients on medication use in the perioperative period

The RA patients use a wide range of medications which may affect their health during surgery and in the postoperative period. The most universally prescribed drugs are NSAIDs, GCs, synthetic DMARDs and biological agents. Most drugs are used in combination therapy [23]. According to certain authors, the number of RA patients subject to arthroplasty while taking regular or biological DMARDs varies from 75% to 84%. In a similar way, GC use in the same group reaches 80% [24].

One of the most widely discussed problems of the RA patients' care is the perioperative regimen of various medications. It should be noted that recommendations as to starting and ceasing the drug use during surgery is forever changing. For instance, in the past it was recommended to suspend the methotrexate use 2 weeks before surgery and resume it 2 weeks afterwards to avoid inflammatory process [25-27]. The same recommendation concerned Leflunomide [28]. The recent guidelines do not include this recommendation; however, it remains debatable [29, 30].

It is essential to recognize that every patient requires his/her own customized care. It is also vital that a rheumatologist, surgeon/orthopedist and possibly infectionist should perform a joint assessment of the required therapy for the individual RA patients in the perioperative period. Regimen modification during the perioperative period may result in the deterioration of patient's health and complication occurrence. This is why it is important to discuss the alternative drug replacements for those whose use was ceased in the perioperative period. It would potentially reduce the adverse effect of cessation and promote a rapid recovery.

Recommendations on non-steroid anti-inflammatory drugs and acetylsalicylic acid (ASA)

Using the NSAIDs to treat the RA symptoms is fairly common. Due to the non-selective inhibiting effect on Thromboxane A₂ (TXA₂) during the platelet aggregation, there is an elevated risk of surgical

hemorrhage; the NSAIDs, especially Coxibs, should thus be ceased in the perioperative period. With the NSAIDs, the platelet function is reversibly inhibited and returns to normal by the time the drug is half-eliminated. NSAIDs have various durations of elimination half-life: from 2 to 6 hours (Ibuprofen, Ketoprofen, Indometacin) to 7–15 hours (Celecoxib, Naproxen) and up to > 20 hours (Meloxicam, Nabumetone, Piroxicam) [31]. It is advisable that the NSAIDs be suspended pending the surgery for a period equal to 5 elimination half-lives in order to ensure the return to a sustainable homeostasis and resumed 2–3 days after the surgery [32].

Selective COX-2 inhibitors, also known as Coxibs, were developed in order to bring to a minimum the gastrointestinal side effects and, presumably, do not pose a significant risk of perioperative bleeding [31]. However, the Coxibs and highly-selective COX-2 inhibitors significantly increase the risk of cardiovascular events [33]. The Coxibs are not recommended for patients with a high cardiovascular risk or thrombophilia [33]. A recent study reports one of Coxibs – Celecoxib – to provide the same degree of cardiovascular safety as Ibuprofen or Naproxen if prescribed in a moderate/low dose [34].

Animal studies show that the COX-2 inhibitors may have adverse effect on tendon healing [35], possibly due to prostaglandin synthesis inhibition, as the latter are responsible for the bone formation, increase of osteoblast proliferation and differentiation [36].

Taking into account the above mentioned findings, it should be noted that NSAID perioperative use should be carefully assessed and restricted in the RA patients due to the elevated risk of cardiovascular events and presumable NSAID interference with wound healing, which may be aggravated in the RA patients due to DMARD and GC use. Combined Paracetamol and opioid use in the perioperative period may be a safe and effective NSAID alternative [37].

Aspirin (acetylsalicylic acid (ASA)) gets irreversibly bound with platelet cyclooxygenase (COX), and thus the platelet aggregation resumes irrespective of drug's elimination half-life. Megakaryocyte function is recovered due to the auto-production via the totipotent stem cells regulated by thrombopoietin (THPO) from the liver and kidneys. Based on this fact, some researchers, concerned about the perioperative hemorrhage, recommend the aspirin's cessation 10 days before surgery in order to ensure the appropriate platelet formation [2]. However, a major retrospective study by N. R. Smilowitz et al. (2016) reports no connection of aspirin use with an elevated risk of hemorrhage in the perioperative period [38]. The American College of Chest Physicians (ACCP) and American College of Cardiology/American Heart Association (ACC/AHA) recommend continuing use

of Aspirin for the patients with a moderate to high risk of cardiovascular events if Aspirin is used as a secondary preventive means before the planned surgery [39, 40]. Such patients include subjects with an ischemic heart disease, congested heart failure, diabetes mellitus, renal failure or cerebrovascular condition [39]. However, the RA alone poses no risk of cardiovascular event. This is why, taking into account the low risk of Aspirin-provoked life-threatening hemorrhage, this drug may be continued and recommended for the RA patients in treatment, if there are no severe contraindications [39, 40].

Beta blockers should be continued by those patients who get them on a regular basis [40]. The Beta blockers prescribed to control the heart rate and provide the anti-ischemic effect, along with the statins – to reduce the endothelial damage risk, may provide additional protection for the RA patients with CVDs [40].

Conventional Synthetic Disease-Modifying Drugs (csDMARDs)

In the recent years, the principles of RA treatment have been changing significantly in order to incorporate a major breakthrough in pathogenesis understanding. The synthetic DMARDs (sDMARDs) are among the most common medications prescribed to the RA patients, namely Methotrexate (MTX), Sulfasalazine (SSZ), Leflunomide and Hydroxychloroquine (HCQ) [24].

Their mechanisms of action vary to such an extent that an orthopedic surgeon is obliged to understand how the pharmacokinetics may affect the patient's health during the surgery. Methotrexate (MTX) is capable of inhibiting Dihydrofolate reductase (DHFR), and the latter, by means of tetrahydrofolate concentration's reduction, causes purine and pyrimidine synthesis inhibition. Methotrexate (MTX) has a number of side effects, including hemopoiesis inhibition, hepatotoxicity and an elevated risk of infection developing. This is why the Methotrexate (MTX), being the Dihydrofolate reductase (DHFR) inhibitor, should be complemented by folic acid [41]. According to the recent studies, the Methotrexate (MTX) has no side effects in the perioperative period, and its use should not be ceased before and during the surgery [24, 29, 30]. This claim has been supported by the latest Guidelines co-authored by the American College of Rheumatology (ACR), American Association of Hip and Knee Surgeons (AAHK) and British Society for Rheumatology [29]. There was one exception: a patient with a slowed-down consolidation or non-union. The reference sources contain controversial opinions on whether the Methotrexate (MTX) causes the osteoblast inhibition. In light of this controversy, some sources still recommend ceasing Methotrexate

(MTX) 1 week before the surgery and resume it 1-2 weeks afterwards [25-27].

The Sulfasalazine (SSZ) inhibits a *de novo* pyrimidine synthesis due to a selective inhibiting the Dihydroorotate dehydrogenase (DHODH); it is a combination of 5-aminosalicylic acid (5-ASA) and Sulfapyridine. At first, the Sulfasalazine (SSZ) was prescribed to the RA patients because it has an anti-inflammatory and anti-microbe effect; however it is still used quite actively in combination with other DMARDs [42]. The ACR and AAHK recommend using the Sulfasalazine (SSZ) during the entire perioperative period, without pausing [29].

Although the Hydroxychloroquine (HCQ) is mostly known for its antimalarial action, it is also used in the RA treatment. Its mechanism is based on the lysosomal inhibition, antigene presentation and the Toll-like receptor signal transmitter [43]. The studies show multiple positive effects for the RA patients: lipid profile normalizing, CVD risk, diabetes incidence and general incidence of cardiovascular event reduction [43]. The ACR and AAHK recommend using the Hydroxychloroquine (HCQ) during the entire perioperative period, without pausing for surgical intervention [29].

The findings obtained on the Leflunomide use are contradictory [44-46]. A significant increase of infectious complications to the surgery incision, slowed-down healing was registered in those patients taking the Leflunomide, compared with those taking the Methotrexate (MTX) [47]. However, there were no differences found in the infectious complications between the patients continuing to use the Leflunomide and those ceasing it 1 month before the surgery [48]. It is no wonder that recommendations on the perioperative Leflunomide use vary [28]. M. Müller and W. Pippi-Ludwig (2014) suggested continuing the Leflunomide in those patients subjected to the low-risk interventions, while, in case of high-risk interventions, it should be complemented by Colestyramine [49]. The latter point was supported by the recent ACR and AAHK's Guidelines suggesting the continued Leflunomide use for the RA patients in the perioperative period [29].

Glucocorticoid (GC) use

In the recent studies, the Glucocorticoids (GC) yielded their prominence to the DMARDs as far as the perioperative period was concerned. The most severe potential complications associated with the GC use and dependent on their dose are surgical infections, slow healing, bone density reduction and hemodynamic instability, secondary to the adrenal failure [50, 51].

The smallest GC dose promoting immunosuppression and hypothalamic-pituitary-adrenal suppression

has been discussed for a long time and undecided yet [52]. There is evidence that a Prednisone dose of 20 mg during 5 days is enough to inhibit the endogenic Cortisol synthesis [52]. It was determined that the postoperative infection risk was about twice as high for the patients on a daily Prednisone dose of over 10 mg during 3 months before surgery [53], while patients on a daily Prednisone dose of over 15 mg for 1 year are subject to infectious complication risk of 20 times higher than the rest of population subject to arthroplasty; articular infection incidence being 2.5–3 times higher than that of population in general [52]. Thus, a daily Prednisone dose of fewer than 10 mg is safer in the perioperative period than the one over 10 mg.

The patients receiving a continuous GC treatment require high GC doses, also known as a *stress dose*, pending surgery because of a concern that acute adrenal failure may develop [54]. Indispensability of the GC preoperative dose has long been under discussion. As of today, there is no evidence of an elevated risk of side effects, requiring a stress dose, instead of a regular one [55]. However, there are no facts supporting the concept of an elevated GC dose possibly reducing the hemodynamic instability of the RA patients after a major orthopedic intervention in comparison to the patients receiving a regular daily Prednisone dose of ≤ 15 mg [56].

Taking into account the above mentioned facts, the ACR and AAHK do not recommend a stress GC dose before surgery if the patients continue taking regular GC doses. The latter, if possible, should be reduced to < 20 mg of Prednisone per day before the surgery [29]. However, the RA patients receiving a continuous GC treatment should be carefully monitored and receive additional steroid doses if they manifest signs of hemodynamic instability, such as hypotension or tachycardia [56]. These recommendations do not include patients with a primary adrenal failure and hypothalamic disorder [56].

The patients receiving a daily steroid dose of Prednisone > 10 mg and unable of reducing it due to their disease aggravation risk should be provided with a sterile care, careful intraoperative skin treatment, complete wound closure and thorough antibiotic prevention [57]. Other non-pharmacologic strategies, such as antibiotic-impregnated bone cement, were offered 10 years ago to be provided to the patients with a high risk of perioperative infection predisposal, and widely used in the recent times [58].

The patients on high GC doses, pending the planned surgery, should postpone it, if possible, until a better disease control and a daily GC dose reduction to < 20 mg of the equivalent Prednisone dose [29].

It is absolutely necessary that the surgeon should have a discussion on GC perioperative use with the patient, rheumatologist and anesthesiologist in order

to prevent the hypotension associated with an endogenous adrenal function in those patients receiving daily steroid treatment.

Biological Disease-Modifying Antirheumatic Drugs (bDMARD)

The bDMARDs is a large group of modern drugs including 5 tumor necrosis factor alpha (TNF- α) inhibitors (Infliximab, Adalimumab, Etanercept, Certolizumab pegol, Golimumab), T cell co-stimulation inhibitor (Abatacept), anti-B-cell therapy drug (Rituximab), monoclonal antibody blocking interleukin (IL)-6 (Tocilizumab) and IL-1 inhibitor (Anakinra) [29]. The bDMARDs caused a breakthrough in the RA treatment, radically improved the outcomes. They also played a significant role in the RA patient perioperative care.

Postoperative infection risk of the patients receiving biological therapy

It is known that the bDMARDs are associated with infection risk in the non-surgical environment [59], affecting skin, soft tissues and Staphylococcus colonization [60]. The risk is especially prominent in the first months after the biological therapy onset, which may be explained by a higher disease activity and GC dosage ('bridge'-therapy) at the beginning [61].

The bDMARDs have different mechanisms and certain discrepancies in the extent of infection risks; however, at the moment there are few facts conclusively supporting the clinically significant difference in the infection risks among various biological drugs [62]. Initial findings show that the postoperative infection risk is similar for the patients receiving different biological agents [63]. Although the TNF inhibitors belong to the 'oldest' group of drugs, most thoroughly studied and commonly prescribed, the data on perioperative risk associated with the bDMARD use are mainly obtained from their observations.

Several observational trials assessed the postoperative infection risks of the RA patients treated with TNF inhibitors and those untreated with biological agents. S. M. Goodman et al. (2016) [64] performed a meta-analysis of the studies involving in total 7991 RA patients subjected to a major orthopedic surgery. The patients receiving TNF inhibitors had a higher incidence of surface and deep wound infection compared with the patients untreated with biological agents [OR 2.47 95 % confidence interval (CI) (1.66-3.68)]. A further meta-analysis by C. Mabile et al. (2017) provided similar findings [65]. In a very recent one by R. L. Cordtz et al. (2018) [1], the risk of prosthetic joint infection (PJI) was assessed in the RA patients treated and untreated with biological agents for 90 days after hip and knee re-

placement. Authors studied several Danish registers. It was ascertained that the PJI incidence was higher in the patients on biological therapy (2.8 vs. 1.9 per 100 person years for patients treated and untreated with biological agents), though the difference was not statistically significant [adjusted OR 1.61 95 % CI (0.70-3.69)]. Furthermore, it should be noted that the patients on the bDMARDs had a higher disease activity and were presumably prescribed GCs and immunosuppressants pending surgery. It is interesting that the infection incidence was higher in the GC patients [adjusted OR 2.12 95 % CI (0.90-4.98)] and those with a higher disease activity, according to DAS28 [adjusted OR 2.00 95 % CI (1.28-3.13)]. GCs and the RA activity (though not the biological agent use) were also associated with a higher mortality risk 1 year after surgery.

Perioperative care of patients receiving biological therapy

Although the previous researchers expressed their concerns about the postoperative infection risks of the patients on biological therapy, the clinicians are regularly facing a different problem: whether this risk might be reduced by ceasing/suspending the biologic use before surgery. Most studies are comparing patients receiving and not receiving biological therapy; however, these groups differ dramatically in terms of disease activity, comorbidities and treatment (including GC use). As a result, even the most sophisticated statistical methods fail to create the completely matched groups.

As the severe postoperative infection cases are relatively rare (risk of prosthetic joint infection (PJI) is approximately 1 %), at the moment it is impossible to perform a randomized study of patients in order to make a decision whether it is preferable to cease or continue biological treatment. To detect a moderate difference in severe infection incidence (for instance, 5 vs. 7 %) or PJI incidence (for instance, 1 vs. 2 %), the researchers need to recruit a sample of over 4000 subjects.

However, several recent observational studies dealt with tentative timelines of biological therapy and describing the role that a preoperative cessation plays. A. Zahr et al. (2015) [66] assessed the status of 6024 RA patients on the bDMARD, including 896 subjects on biological drugs who had undergone surgery. Neither conventional (synthetic) DMARD, nor bDMARD cessation resulted in the postoperative infection risk reduction.

In order to solve the problems associated with determining exact duration of the biological agent's action and setting deadline or the preoperative cessation, a study group headed by M. D. George (2017) recruited 4288 patients with hip and knee re-

placements. They were given an Infliximab infusion 6 months before the surgery [53]. It was determined that the patients who received Infliximab 4 weeks prior to the surgery had no difference in 30-day or 1-year risk of prosthetic joint postoperative infection compared to patients who were last prescribed Infliximab at least one interval (8–12 weeks) before surgery [OR 0.90 95 % CI (0.60–1.34) and OR 0.98 95 % CI (0.52–1.87), for both outcomes respectively]. The study controlled a number of other potential factors, such as comorbidities, treatment manipulations and other prescriptions.

An interesting study of 311 patients with an inflammatory bowel disease, having undergone abdominal surgery, assessed an association between an Infliximab dose and postoperative infection risk [67]. High Infliximab levels of at least 3 mg/ml were associated with a higher infection risk, though only in patients with Crohn's disease, not with ulcerative colitis.

The small studies of patients on Tocilizumab [68] and Rituximab [69] did not yield enough findings in order to assess the infection risks thoroughly; however, the authors noted that the infection risk was not

associated with the time span between the last Rituximab or Tocilizumab infusion and the surgery. Similar results were obtained in the French register assessment involving 263 patients on the IV Abatacept who were subject to surgical interventions. It was revealed that the preoperative Abatacept use did not reflect on complication risk, although the sample was small and the detection capacity limited [70]. Initial findings of the study involving 1537 patients with hip and knee replacements who were using the IV Abatacept describe a similar picture: patients receiving Abatacept 4 weeks prior to the surgery had no difference of postoperative infection incidence and re-hospitalization compared to the patients receiving Abatacept over 4 weeks prior to the surgery [71]. These findings prove that a long-term cessation of biological treatment does not provide a significant improvement.

Existing studies and meta-analyses of major observation trials do not yield any conclusive evidence as to the appropriate tolerance to the biological treatment and the latter's effect on the severe infection risk. However, we may assume that the biological treatment cessation does not bring any substantial benefits.

Table 1. Specifics of the perioperative drug treatment for the RA patients. Our adaptation of [29]

Synthetic DMARDs	Order of administration	Preoperative tactics
Continue therapy before surgery		
Methotrexate	Once a week	Continue
Sulfasalazine and	Once or twice a day	Continue
Hydroxychloroquine	Once or twice a day	Continue
Leflunomide	Daily	Continue
Biological DMARDs	Order of administration	Perform surgery after drug cessation
Cease one administration, resume therapy 14 days after surgery if there are no signs of bleeding or infection		
Adalimumab	Once a week or once in 2 weeks	During 2 nd or 3 rd week
Etanercept	Once a week or once in 2 weeks	During 2 nd week
Golimumab	Every 4 weeks (percutaneous) Every 8 weeks (intravenous)	During 5 th week During 9 th week
Infliximab	Every 4, 6 or 8 weeks	During 5 th , 7 th or 9 th week
Abatacept	Once a month (intravenous) Once a week (percutaneous)	During 5 th week During 2 nd week
Certolizumab pegol	Every 2 or 4 weeks	During 3 rd or 5 th week
Rituximab	2 doses during 2 weeks, after that every 4–6 months	During 7 th month
Tocilizumab	Once a week (percutaneous) Once every 4 weeks (intravenous)	During 2 nd week During 5 th week
Anakinra	Daily	During 2 nd day
Secukinumab	Once every 4 weeks	During 5 th week
Ustekinumab	Once every 12 weeks	During 13 th week
Tofacitinib	Once or twice a day	7 days after the final dose

Note: DMARDs — disease-modifying anti-rheumatic drugs

Due to a known bDMARD-related infection risk, ACR/AAHKS group suggests suspending all the prescribed bDMARDs by the planned surgical intervention so that there is a suspension of one drug administration before surgery [29]. For this recommendation to be implemented, a dosing interval rather than an elimination half-life was taken into account, as the elimination half-life does not correlate with duration of the drug's use. In accordance with these guidelines, a patient receiving Infliximab every 8 weeks should get its last dose 9 weeks before surgery, while a patient receiving Adalimumab every 2 weeks, should get the last dose 3 weeks before surgery. Resuming biological treatment should take place 14 days after surgery if the postoperative wound is healing well and there are no signs of local or systemic infection. In their amended recommendations on the bDMARD biological safety, the British Society for Rheumatology (BSR) took a similar approach recommending cessation of the bDMARDs for one interval of administration; it concerns most biological drugs except 2-week percutaneous and 4-week intravenous administration of Tocilizumab and 3-6-month administration of Infliximab). In case of surgical interventions, the patients of high risk group should consider cessation for 3-5 elimination half-lives (if this period is longer than one dosing interval) [30]. The Table presents the deadlines of cessation and resumption of the bDMARD treatment for the RA patients in the perioperative period.

Conclusions

A thorough perioperative assessment of the RA patient is essential in order to achieve positive outcomes in the postoperative period and further management. A carefully collected history, physical examinations

with a relevant laboratory assessment of the organic and systemic functions, differential comorbidity analysis make up this approach. It is advisable to inform the patients about the potential surgical risks, namely an elevated infection risk, slowed-down healing and the VTE events, as well as possible cardiovascular, pulmonary and neurological disorders related to the surgery.

The recent clinical studies improved our understanding of the optimal perioperative RA patient management, although biological therapy remains a contested issue. The latest findings prove that the RA patients face a higher infection risk after surgery; however, drug prescriptions are likely to be only a tip of the iceberg. The DMARD management in the preoperative period should be performed in accordance with the major leading rheumatologic societies' recommendations; furthermore, the approach should be patient-customized by the multi-disciplinary team. The guidelines set a starting point to discuss the issue of perioperative risk minimization; however, the facts should be interpreted taking into account every individual patient. At the moment, the guidelines support a continued use of conventional synthetic disease-modifying drugs during the entire perioperative period and recommend short cessation stints for one dosing period before the surgery with its resumption 14 days after.

It may seem that the principal approach consists in ceasing biological therapy before the surgical intervention despite numerous modern studies dismissing any visible benefit from this strategy. This approach is sensible for many patients though for some of them the bDMARD cessation would not minimize risks in the best possible way. For instance, those patients

Рисунок 1. Алгоритм периоперационного ведения пациентов с ревматоидным артритом (адаптировано нами по [72])

Примечания: бБМАРП — биологические болезньмодифицирующие антиревматические препараты; ГК — глюкокортикоиды; сБМАРП — синтетические болезньмодифицирующие антиревматические препараты.

who often suffer from aggravations of their disease and require high glucocorticoid doses may show better results in the perioperative period if the biological treatment continues rather than ceases. For others, concerns about the postoperative aggravations may overweigh the issue of possible infection, especially if the surgery is low-risk and no prosthetic material is involved. On the contrary, the patients with a long-term remission, though having a history of multiple infections, may probably improve due to cessation. Fortunately, ceasing treatment 1 dosing interval before surgery and resuming it 14 days after (as the recent guidelines suggest) amount to a short-term suspension for most patients. The observation data undoubtedly prove the hypothesis of the longer-term cessation's uselessness.

Despite the contested nature of biological treatment cessation in the perioperative period, there is a consensus that the high glucocorticoid doses bring a significant infection risk. These findings suggest that a long-term cessation may be counter-productive, as the potential aggravation will bring a glucocorticoid prescription. The data also support the aim of glucocorticoid dose reduction up to the surgical intervention, if possible.

It should be emphasized that the higher doses of glucocorticoids presumably play a significantly greater negative role in the postoperative infection risk than the biological treatment. Although the ACR recommends avoiding any planned surgery for the patients requiring Prednisone in a daily dose of over 20 mg, the risk grows even with the lower doses. Every effort should be made in order to reduce the glucocorticoid dose to a minimum before surgery. The more recent findings support the claim that a long-term cessation of biological therapy does not improve the outcomes and that restricting the glucocorticoid effect by cutting the daily Prednisone dose to < 20 mg before surgery is essential. The patients receiving higher doses should consider a possibility of the planned surgery postponement until the disease activity lessens. This suggested approach to the RA patient treatment if subject to the prior surgery is based on the extant data and guidelines and presented at the Figure below.

In this way, the extant guidelines may help the RA patients awaiting the surgery. There are ongoing studies likely to shed light on these patients' management in the nearest future.

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Менеджмент пацієнтів з ревматоїдним артритом у періопераційному періоді

Резюме. Пацієнти з ревматоїдним артритом (РА), незважаючи на успіх консервативної терапії, мають високу потребу у проведенні ортопедичних хірургічних втручань, а також операцій за соматичними показаннями. Таким пацієнтам необ-

хідна ретельна періопераційна оцінка та підготовка для досягнення сприятливих результатів оперативного лікування й менеджменту в післяопераційному періоді. Повинен бути зібраний детальний анамнез, проведено детальне фізикальне об-

стеження з відповідною лабораторною оцінкою функції органів і систем, з диференціюванням ураження органів, вторинного щодо РА або пов'язаного з коморбідними станами. Слід поінформувати пацієнтів про потенційні ризики хірургічного втручання, зокрема підвищення ризику інфікування, уповільнення загоєння ран і розвиток венозних тромбоемболій, а також про основні можливі серцево-судинні, легеневі й неврологічні порушення, що можуть бути зумовлені хірургічним втручанням. В оглядовій статті підбито підсумки останніх досягнень у цій галузі та розглянуто останні рекомендації, запропоновані Американською колегією ревматологів і Американською асоціацією хірургів, щодо періопераційного ведення й тактики антиревматичної терапії в пацієнтів перед тотальним ендопротезуванням колінних і кульшових суглобів 2017 року і керівництво з біологічної безпеки хворобомодифікуючих антиревматичних препаратів (ХМАРП) Британського товариства ревматологів при запальних артритих. Менеджмент ХМАРП у передопераційному періоді має здійснюватися згідно з рекомендаціями основних провідних ревматологічних спільнот, але підхід повинен бути індивідуалізова-

ний, із залученням мультидисциплінарної команди. На сьогодні рекомендації підтримують продовження прийому синтетичних ХМАРП упродовж усього періопераційного періоду й рекомендують короткочасне переривання біологічної терапії на один інтервал дозування перед операцією з продовженням прийому через 14 днів після операції. Більш високі дози глюкокортикоїдів роблять значно більший внесок у ризик післяопераційної інфекції, аніж біологічна терапія. Рекомендують уникати планової операції в пацієнтів, які приймають преднізолон в дозі більше за 20 мг/д. Рекомендують зниження дози глюкокортикоїдів до мінімально можливої перед операцією. Незважаючи на те, що невизначеність залишається, ці недавні дослідження та рекомендації дозволяють більш раціонально і науково обґрунтовано підходити до ведення пацієнтів з РА, яким заплановано хірургічне втручання або яким необхідно провести її терміново.

Ключові слова: періопераційний менеджмент; ревматоїдний артрит; ендопротезування суглобів; інфекція; ризик; хворобомодифікуючі антиревматичні препарати; глюкокортикоїди; біологічна терапія; інгібітори фактора некрозу пухлини

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Менеджмент пациентов с ревматоидным артритом в периоперационном периоде

Резюме. Пациенты с ревматоидным артритом (РА), несмотря на успех консервативной терапии, имеют высокую потребность в ортопедических хирургических вмешательствах, а также в операциях по соматическим показаниям. Эти пациенты нуждаются в тщательной периоперационной оценке и подготовке для достижения благоприятных результатов оперативного лечения и менеджмента в послеоперационном периоде. Должен быть тщательно собран анамнез, проведено скрупулезное физическое обследование с соответствующей лабораторной оценкой функций органов и систем, дифференциацией вторичных поражений органов или коморбидных состояний. Пациенты должны быть проинформированы о потенциальных рисках хирургического вмешательства, включая повышенный риск инфицирования, замедления заживления ран и венозной тромбоемболии, а также об основных возможных сердечно-сосудистых, легочных и неврологических нарушениях, которые могут быть вызваны хирургическим вмешательством. В обзорной статье подведены итоги последних достижений в этой области и рассмотрены последние рекомендации, предложенные Американской коллегией ревматологов и Американской ассоциацией хирургов, по поводу периоперационного ведения и тактики антиревматической терапии у пациентов перед тотальным эндопротезированием коленных и тазобедренных суставов 2017 года и руководство по биологической безопасности болезньюмодифицирующих антиревматических препаратов (БМАРП) Британского общества ревма-

тологов при воспалительных артритих. Назначение БМАРП в предоперационном периоде должно осуществляться в соответствии с рекомендациями основных ведущих ревматологических сообществ, но подход должен быть индивидуализированным, с привлечением многопрофильной команды. Сегодня рекомендации поддерживают продолжение приема синтетических БМАРП на протяжении всего периоперационного периода и рекомендуют кратковременное прерывание биологической терапии на один интервал дозировки перед операцией с продолжением приема через 14 дней после операции. Более высокие дозы глюкокортикоидов вносят значительно больший вклад в риск послеоперационной инфекции, чем биологическая терапия. Рекомендуют избегать плановой операции у пациентов, получающих преднизолон в дозе более 20 мг/д. До операции рекомендуется снизить дозу глюкокортикоидов до минимально возможного уровня. Несмотря на то, что неопределенность остается, эти недавние исследования и рекомендации позволяют более рационально и научно обоснованно подходить к ведению пациентов с РА, которым запланировано хирургическое вмешательство или которым необходимо провести его срочно.

Ключевые слова: периоперационный менеджмент; ревматоидный артрит; эндопротезирование суставов; инфекция; риск; болезньюмодифицирующие антиревматические препараты; глюкокортикоиды; биологическая терапия; ингибиторы фактора некроза опухоли