Slovak international scientific journal

№72, 2023
Slovak international scientific journal

The journal has a certificate of registration at the International Centre in Paris – ISSN 5782-5319.
The frequency of publication – 12 times per year.
Reception of articles in the journal – on the daily basis.
The output of journal is monthly scheduled.
Languages: all articles are published in the language of writing by the author.
The format of the journal is A4, coated paper, matte laminated cover.
Articles published in the journal have the status of international publication.

The Editorial Board of the journal:
Editor in chief – Boleslav Motko (Bratislava) Slovakia
The secretary of the journal – Milica Kovacova (Bratislava) Slovakia

- Lucia Janicka – (Bratislava) Slovakia
- Stanislav Čerňák – (Bratislava) Slovakia
- Miroslav Výtisk – (Nitra) Slovakia
- Dušan Igaz – (Nitra) Slovakia
- Terézia Mészárosová – (Banská Bystrica) Slovakia
- Peter Masaryk – (Rzeszów) Poland
- Filip Kocisov – (Wrocław) Poland
- Andrej Bujalski – (Košice) Slovakia
- Jaroslav Kovac – (Trnava) Slovakia
- Paweł Miklo – (Bratislava) Slovakia
- Jozef Molnár – (Bratislava) Slovakia
- Tomajko Milaslavski – (Nitra) Slovakia
- Natália Jurková – (Bratislava) Slovakia
- Jan Adamczyk – (Prague) Czech Republic
- Boris Belier – (Bratislava) Slovakia
- Stefan Fišan – (Bratislava) Slovakia
- Terézia Majercakova – (Wien) Austria
- Ekaterina Semko (Kyiv) Ukraine

1000 copies
Slovak international scientific journal
Partizanska, 1248/2
Bratislava, Slovakia 811 03
email: info@sis-journal.com
site: http://sis-journal.com

NORMAL AND PATHOLOGICAL PHYSIOLOGY

PEDAGOGY

PHILOLOGY

PHILOSOPHY

STATE AND LAW

NORMAL AND PATHOLOGICAL PHYSIOLOGY

FEATURES OF PHARMACOTHERAPY AND ITS MAIN SIDE EFFECTS IN RHEUMATOID ARTHRITIS
(Literature review)

Bukach O.,
assistant of the department of internal medicine
Zhyho O.,
Strila Z.,
Strelchuk O.
Bukovyna State Medical University

Abstract

Despite significant progress in establishing the causes, mechanisms of occurrence, approaches to diagnosis and treatment, rheumatoid arthritis remains one of the most widespread and prognostically unfavorable diseases. It is known that rheumatoid arthritis is a chronic multifactorial systemic disease of connective tissue, with symmetrical damage to small joints, according to the type of erosive-destructive polyarthritis and the presence of extra-articular manifestations.

Early diagnosis of the disease is difficult, since immunopathological changes with a subclinical course occur long before the appearance of clinical manifestations of the disease. Therefore, establishing a diagnosis in the first months of the disease is decisive for its further progression, prognosis, long-term consequences of rheumatoid arthritis and the correct appointment of treatment.

Keywords: rheumatoid arthritis, disease-modifying antirheumatic drugs, glucocorticosteroids, nonsteroidal anti-inflammatory drugs, biological therapy, multidisciplinary approach.

Ensuring adequate quality of life, increasing its duration, and reducing disability and mortality in patients with RA remains an unsolved problem [1]. Achieving this goal depends on timely diagnosis and rationally selected pharmacotherapy regimens, primarily with the use of disease-modifying antirheumatic drugs (DMARDs), glucocorticosteroids (GCS), and nonsteroidal anti-inflammatory drugs (NSAIDs) [2]. Pharmacotherapy does not always lead to remission, does not stop the progression of the disease, and at the same time has a number of side effects that cause the occurrence of concomitant diseases, burdening the clinical course and complicating the diagnosis of RA.

To achieve the optimal effect of RA treatment, it is necessary to adhere to a multidisciplinary approach, which consists in the use of pharmacotherapy, diet therapy, psychotherapy, physical therapy (PE), physiotherapy, sanatorium-resort treatment, and surgical correction of joints while simultaneously increasing the patient's level of education about his disease [3].

According to the modern treatment paradigm, the basis of pathogenetic treatment is DMARDs (cytostatics, leflunomide, sulfonamides, gold preparations, aminoquinoline derivatives, immunomodulators and biological agents) [4], which should be prescribed at the stage of early and very early RA [5], in order to achieve remission or minimal disease activity and prevention of joint destruction [6]. The choice of DMARDs and dose depends on the radiological stage and activity of the process [7].

Currently, early "aggressive" basic therapy is recommended, which quickly suppresses the immunoinflammatory process, prevents the development of cartilage destruction, as a result of which there is a high probability of achieving a stable remission [8].

Despite the introduction into clinical practice of biological agents (infliximab, etanercept, adalimumab, rituximab, anakinra, etc.) [9] and new DMARDs (mofetil, mycophenolate), the "gold standard" of RA treatment remains MT [10]. According to the results of many randomized studies PROMPT, IMPROVED, DREAM, CAMERA, CAMERA-II, it has been confirmed that MT is a starting drug in the treatment of RA [11]. MT metabolites contribute to the release of adenosine, which in high concentrations reduces platelet aggregation and has anti-inflammatory activity. Adenosine inhibits the proliferation of endothelial cells, the growth of synovial fibroblasts, the adhesion and migration of leukocytes through the vascular wall to the inflammatory zone, the production of toxic oxygen metabolites, leukotrienes, TNF-α, IL-1 and IL-8. At the same time, the synthesis of anti-inflammatory cytokines IL-4 and IL-10 increases, which reduce the number of activated T cells. As a result, the drug has a cytotoxic effect, inhibiting DNA synthesis and repair [12].

The results of the SAVE study showed a slowing down of the progression of undifferentiated arthritis in RA when treated with MT. At the same time, with the complex use of GCS and biologically active substances (BAR) (infliximab), no slowing down of the progression of undifferentiated arthritis in RA was observed, in contrast to MT [13].

According to the results of randomized studies within the framework of the DREAM program, in 534 patients with very early and active RA, it was established that the use of MT allowed to significantly increase the effectiveness of RA therapy, compared to a control group of patients who received treatment according to the standard of routine clinical practice. In 10% of patients, insufficient effectiveness of MT was

observed, therefore, the treatment scheme sequentially included sulfasalazine, adalimumab, and infliximab in combination with MT [14].

The question regarding the starting dose of MT and the pace of its increase to the maximum remains unresolved. It is believed that the use of MT in high starting doses (25 mg/week) allows to achieve control over the progression of RA, but it causes a number of adverse reactions and is also characterized by low patient compliance [15].

According to the unified clinical protocol [16], the dose of MT should be 10–15 mg/week with a further increase in the dose by 5 mg every 2–4 weeks to 20–25 mg/week.

Analysis of the results of the study proved that MT should be prescribed at a starting dose of 7.5 mg, followed by an increase to the maximum dose (20 mg/week in the 8th week of treatment), thanks to which clinical remission of RA was achieved [17].

In the study of G.S. Hazlewood et al. [18] proved the safety of using a starting dose of 25 mg/week MT. At the same time, the number of side effects was comparable to patients who received 7.5 mg/week of this drug.

According to the results of the prospective study CAMERA, BEST, it was found that increasing the dose of MT from 15 mg/week to 20-25 mg/week (by 5 mg/month) leads to an increase in the effectiveness of treatment, but with a higher frequency of adverse reactions, unlike slow increase in the dose of MT (by 5 mg/3 months). However, against the background of taking MT, it is necessary to prescribe folic acid in a dose equal to half the weekly dose of this drug and no earlier than a day after and no later than a day before its next administration. According to the level of evidence A, MT is recognized as the best among other DMARDs in relation to the efficiency-toxicity ratio. Treatment with this drug is stopped in 30-40% due to the occurrence of side effects and the development of the phenomenon of secondary resistance over 3-7 years, and not because of its ineffectiveness [19].

The most common side effects of MT are: hepatotoxicity, gastrointestinal disorders (25%), ulcerative stomatitis (15%), headache (10%), severe infections, skin rash, less often alopecia, myelosuppression, pneumonitis. intestinal tract (GI) should be switched to parenteral administration (intramuscular or subcutaneous) MT [20].

Therefore, according to the results of 97 randomized clinical trials in which 14,159 patients were involved, the effectiveness of MT as a starting drug is not in doubt, because thanks to its use it is possible to achieve more effective control of RA symptoms and prevent the progression of joint destruction than when using other DMARDs, with less toxicity [21].

Combined therapy of RA is prescribed in case of inadequate response to MT monotherapy, high disease activity, unfavorable and rapidly progressing course of RA, and at the stage of pronounced erosive joint changes [22]. According to the recommendations of EULAR and ACR, regardless of whether MT monotherapy or combined therapy was performed, complete clinical remission of RA was found in only 15-40% of patients. Therefore, the place of combined basic therapy in the RA treatment system is still not defined, since the development of possible adverse reactions is unpredictable [23].

Treatment of RA with the use of DMARDs should be started as early as possible. Thus, according to the research of F.C. Breedveld [24], which was conducted in Leiden, it was found that when basic drugs were used in the first three months, the activity of the disease was lower than in patients who started therapy 3-6 months after the diagnosis of RA.

These data were also confirmed by Australian scientists O.M. Ragab et al. [25] in patients with "very early" and "early" RA. Treatment of patients with "very early" RA according to ACR20 was effective in about 70%, and with "early" RA in only 40% of patients. Therefore, there is a "therapeutic window" in which treatment with basic drugs is most effective. RA treatment effectiveness is assessed after 1.5-3 months.

As a result of the slow development of the clinical effect of DMARDs, which occurs several weeks-months after the start of treatment, fast-acting anti-inflammatory drugs are used that reduce or eliminate the joint syndrome, but do not affect the course of RA [26].

Such agents include NSAIDs, which have analgesic, antipyretic, anti-inflammatory and antiplatelet effects [27].

NSAIDs are divided into 4 groups depending on selectivity: non-selective inhibitors of cyclooxygenase (COX) - diclofenac, ibuprofen, etc.; selective COX-1 inhibitors – low doses of acetylsalicylic acid; selective COX-2 inhibitors - nimesulide, meloxicam, etc.; highly selective (specific) COX-2 inhibitors - celecoxib, rofecoxib, etc. In terms of effectiveness, NSAIDs do not differ significantly among themselves, but the choice will depend on the safety, tolerability and cost of the drug [28].

The safety of this group of drugs will depend on the occurrence of adverse reactions from the gastrointestinal tract, cardiovascular system (CVS), kidneys, and blood system (inhibition of platelet function) [29].

It has been established that the occurrence of half of all NSAID-gastropathies is caused by taking NSAIDs. Selective inhibitors of COX 2 belong to drugs with evidence level A, which less often cause damage to the gastrointestinal tract. Side effects occur as a result of inhibiting the synthesis of prostaglandins by blocking the cyclooxygenase and lipoxygenase pathways of their metabolism [30]. At the same time, the synthesis and effect of natriuretic peptides decreases, the formation of vasopressin increases, which, in turn, is accompanied by fluid retention and vasospasm. This leads to hyperactivity of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic-adrenal system and an increase in blood pressure [31].

It is recommended to prescribe COX 2 along with low doses of aspirin in patients with cardiovascular complications (CVC) that occurred as a result of taking NSAIDs [32].

Therefore, in connection with the high probability of adverse reactions, NSAIDs should be prescribed only when absolutely necessary, and the choice of the

drug should be made taking into account the initial levels of risk from the gastrointestinal tract and cardiovascular system for a specific patient, according to the recommendations of the European multidisciplinary group of experts regarding the judicious use of NSAIDs in rheumatic diseases (2011).

The best therapeutic effect in patients with RA occurs with the complex use of DMARDs, NSAIDs and GCS. GCS have powerful anti-inflammatory and immunosuppressive effects by suppressing the synthesis of pro-inflammatory cytokines, adhesion molecules and the pro-inflammatory form of cyclooxygenase [33].

According to the results of the BEST study, when using a combination of DMARDs and GCS in early RA, a rapid clinical effect, a slowing of the progression of joint destruction, and a high percentage of the development of remission according to the EULAR criteria were found [34]. However, this group of drugs can cause a number of side effects: aseptic necrosis of large joints, osteoporosis, infectious complications, the occurrence of gastric ulcer and duodenum, psychosis, slow wound healing, and cardiovascular disorders. It is a well-known fact that glucocorticoids contribute to an increase in the level of glucose in the blood ("steroid diabetes"), an increase in appetite and redistribution of adipose tissue in the form of central (abdominal) obesity [35].

In the SAMERA-II and IMPROVED studies, it was found that with the combined therapy of MT and GCS in low doses (10 mg of prednisolone), the remission rate was 72% and was achieved after 5 months, in contrast to MT monotherapy 61%, after 11 months [36].

When using GCS, the risk of hypertension, obesity, insulin resistance, and dyslipidemia arises due to a proatherosclerotic effect, but at the same time, they cause an anti-inflammatory effect, reducing the degree of RA activity, which paradoxically improves the function of the endothelium [37].

In this regard, corticosteroids are used as "bridge therapy", prescribing them for high activity of the disease, ineffectiveness of NSAIDs, rapidly progressing course of the disease with multiple joint damage, for several months before the onset of the effect, followed by a gradual dose reduction until its cancellation [38].

The dose of GCS is selected individually: a daily dose of prednisolone ≤ 7.5 mg is considered safe, which adequately controls inflammation in RA in the absence of adverse reactions [39].

Results of a prospective study by I. Hafstrom, M. Rohani et al. testify that the use of prednisolone at a dose of 7.5 mg for 2 years in patients with RA did not cause endothelial dysfunction, but significantly increased blood pressure and cholesterol concentration. The same results were obtained by Y. Park, C. Ahn et al. [40], who, when using GCS in small doses (less than 10 mg), in patients with RA, an increase in cholesterol level was observed, in contrast to patients who did not receive this drug.

Depending on the degree of activity of RA, GCS is used in the following doses: 15-30 mg/day of prednisolone for an average degree of activity, 40-60 mg/day for a high degree of activity and the development of extra-articular manifestations, with a further decrease by 1/3-1/4 - 1/6 tablet once every 5-7 days before the maintenance dose. At the same time, it is also necessary to take into account the biological rhythms of the adrenal cortex, which determine the use of this drug in the morning hours [41].

A close direct relationship has been established between the dose of GCS, the number of atherosclerotic plaques in the carotid basin and vessel stiffness [42].

With long-term use of GCS in RA for more than 6 months in medium doses (≥7.5 mg/day), there is a high probability of developing hypertension compared to patients who do not use drugs of this group or take them in low doses for a short time [43].

Therefore, the risk of cardiovascular complications is higher in patients who have been taking GCS for a long time and in high doses.

Taking into account the occurrence of osteoporosis in most patients with RA when using GCS, it is recommended to include calcium preparations and group D vitamins in the treatment regimen.

Therefore, the timely detection and treatment of rheumatoid arthritis consists in the use of individualized therapy, namely disease-modifying antirheumatic therapy - methotrexate, together with glucocorticosteroids and non-steroidal anti-inflammatory drugs, which will make it possible to significantly reduce the systemic inflammatory response, improve the patient's prognosis and quality of life, and allow to obtain long remission.

References

1. Kovalenko VM, Kornatskyi VM. Rehionalni osoblyvosti rivnia zdorovia narodu Ukrainy: analitychno-statystychnyi posibnyk. Kyiv; 2011. 165 s.

2. Nemish IL. Suchasni pidkhody do klasyfikatsii, diahnostyky ta likuvannia revmatolohichnykh zakhvoriuvan z pozytsii dokazovoi medytsyny. Ukrainskyi revmatolohichnyi zhurnal. 2022;88(2):4-7.

3. Yaremenko OB, Mykytenko AM. Vlyianye komorbydnosty y systemnыkh proiavlenyi revmatoydnoho artryta na эffektyvnost y perenosymost lechenyia syntetycheskymy bazysnыmy preparatamy. Ukrainskyi revmatolohichnyi zhurnal. 2015;1:28-35.

4. Ma X, Xu S. TNF inhibitor therapy for rheumatoid arthritis. Biomed Rep. 2013 Mar;1(2):177-184.

5. Smolen JS, Lamdewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017 Jun;76(6):960-977. doi: 10.1136/annrheumdis-2016-210715.

6. Ustinov OV. Alhorytm dii likaria pry nadanni medychnoi dopomohy khvorym na revmatoidnyi artryt. Ukrainskyi medychnyi chasopys. 2014;4:1-10.

7. Gaujoux-Viala C, Smolen JS, Landewé R, Dougados M, Kvien TK, Mola EM, et al. Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR rec-

ommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2010 Jun;69(6):1004-9. doi: 10.1136/ard.2009.127225.

8. Kovalenko VN, Bortkevych OP. Yndyvydualyzatsyia lechenyia revmatoydnoho artryta: kurs na dostyzhenye optymalnыkh rezultatov. Ukrainskyi revmatolohichnyi zhurnal. 2011;45(3):5-15.

9. Vizir VA, Buriak VV, Sholokh SH, Zaika IV, Shkolovyi VV. Osnovy diahnostyky, likuvannia ta profilaktyky zakhvoriuvan kistkovomiazovoi systemy ta spoluchnoi tkanyny. Zaporizhzhia;2021. 174 s.

10. Pincus T, Cronstein B, Braun J. Methotrexate – the anchor drug – an introduction. Clin Exp Rheumatol. 2010 Sep-Oct;28(61):S1-2.

11. Burmester GR, Kivitz AJ, Kupper H, Arulmani U, Florentinus S, Goss SL. Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial. Ann Rheum Dis. 2015 Jun;74(6):1037-44. doi: 10.1136/annrheumdis-2013-204769.

12. Smolen JS, Breedveld FC, Burmester GR, Bykerk Vivian, Dougados Maxime, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. 2016 Jan;75(1):3-15. doi: 10.1136/annrheumdis-2015-207524.

13. Machold KP, Landewé R, Smolen JS, Stamm TA, van der Heijde DM, Verpoort KN, et al. The stop arthritis very early (SAVE) trial, an international multicentre, randomised, double-blind, placebo-controlled trial on glucocorticoids in very early arthritis. Ann Rheum Dis. 2010 Mar;69(3):495-502. doi: 10.1136/ard.2009.122473.

14. Vermeer M, Kuper HH, Hoekstra M, Haagsma CJ, Posthumus MD, Brus HL, et al. Implementation of a treat-to-target strategy in very early rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. Arthritis Rheum. 2011 Oct;63(10):2865-72. doi: 10.1002/art.30494.

15. Muravev YuV. Dozyrovanye metotreksata pry lechenyy revmatoydnoho artryta. Nauchno-praktycheskaia revmatolohyia. 2013;51(4):456-459.

16. Pro zatverdzhennia ta vprovadzhennia medyko-tekhnolohichnykh dokumentiv zi standartyzatsii medychnoi dopomohy pry revmatoidnomu artryti. Nakaz MOZ Ukrainy vid 11.04.2014 № 263. Kyiv: MOZ Ukrainy; [Internet]. Kyiv: MOZ Ukrainy; 2014 [tsytovano 2017 Ser 16]. Dostupno: http://www.moz.gov.ua/ua/portal/dn_20140411_0263.html.

17. Rudiuk LI, Kharitonova OM. Farmakoterapiia pry revmatoidnomu artryti: suchasnyi pohliad na problemu. Ukrainskyi revmatolohichnyi zhurnal. 2013;54(4):46-49.

18. Hazlewood GS, Thorne JC, Pope J, Lin D, Tin D, Boire G, et al. The comparative effectiveness of oral methotrexate versus subcutaneous methotrexate for the treatment of early rheumatoid arthritis. Ann Rheum Dis. 2016 Jun;75(6):1003-8. doi: 10.1136/annrheumdis-2014-206504.

19. Shuba NM, Harmysh EA, Kovhanych TA. Byolohycheskaia terapyia v lechenyy revmatoydnoho artryta: teoryia y praktyka. 2017;2:64-5.

20. Neiko YeM, Yatsyshyn RI, Shtefiuk OV, Shtefiuk TI, Shevchuk OS. Pobichni efekty terapii revmatoidnoho artrytu: pohliad na problemu. Ukrainskyi terapevtychnyi zhurnal. 2010;3:90-100.

21. Kuriya B, Arkema EV, Bykerk VP, Keystone EC. Efficacy of initial methotrexate monotherapy versus combination therapy with a biological agent in early rheumatoid arthritis: a meta-analysis of clinical and radiographic remission. Ann Rheum Dis. 2010 Jul;69(7):1298-304. doi: 10.1136/ard.2009.118307.

22. Fleischmann R, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet. 2017 Jun;390:457-468. doi:10.1016/S0140-6736(17)31618-5.

23. Holovach IIu. Metotreksat yak bazovyi preparat u likuvanni revmatoidnoho artrytu: dokazy efektyvnosti ta optymalnoho dozuvannia. Zdorovia Ukrainy. 2013;5:64-6.

24. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER Study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who have not had previous methotrexate treatment. Arthritis Rheum. 2006 Jan;54(1):26-37.

25. Ragab OM, Zayed HS, Abdelaleem EA, Girgis AE. Effect of early treatment with disease-modifying anti-rheumatic drugs and treatment adherence on disease outcome in rheumatoid arthritis patients. Egypt Rheumatol. 2017 Apr;39(2):69-74.

26. Riazanova AIu, Mahnytskaia OV, Horiushkyna AA. Nesteroydnыe protyvovospalytelnыe sredstva kak faktor ryska serdechno-sosudystыkh oslozhnenyi. Lekarstvennыi vestnyk. 2013; 51 (3):40-47.

27. Zub LO, Roborchuk SV. Osoblyvosti medykamentoznoho vplyvu patohenetychnoi ta bazysnoi terapii revmatoidnoho artrytu na stan nyrok. Bukovynskyi medychnyi visnyk. 2015;3(71):231-6.

28. Karateev A. E., Nasonov E. L., Yakhno N. N. V. T. Yvashkyn, N. V. Chychasova, L. Y. Alekseeva y dr. Klynycheskye rekomendatsyy «Ratsyonalnoe prymenenye nesteroydnыkh protyvovospalytelnыkh preparatov (NPVP) v klynycheskoi praktyke». Sovremennaia revmatolohyia. 2015. 26 s.

29. Kotov OV. NPVP: v poyskakh zolotoi seredynы – sootnoshenye «bezopasnost/эffektyvnost». Spravochnyk polyklynycheskoho vracha. 2013;1:15-9.

30. Alemao E, Cawston H, Bourhis F, Al M, Rutten-van Mölken MPMH, Liao KP, Solomon DH. Cardiovascular risk factor management in patients with RA compared to matched non-RA patients. Rheumatology. 2016 May;55(5):809–816. https://doi.org/10.1093/rheumatology/kev427.

31. Zakrytov DO. Kombinovana terapiia statynom ta inhibitorom anhiotenzyn-peretvoriuvalnoho fermentu u khvorykh na arterialnu hipertenziiu i revmatoidnyi artryt. Dosiahnennia biolohii ta medytsyny. 2016;1:42-5.

32. Riazanova AIu, Mahnytskaia OV, Horiushkyna AA. Nesteroydnыe protyvovospalytelnыe sredstva kak faktor ryska serdechno-sosudystыkh oslozhnenyi. Lekarstvennыi vestnyk. 2013; 51 (3):40-47.

33. Sydorchuk II. Kaspruk NM, Koval HD, Liashuk RP, Moroziuk YaV, Yakovets KI. Syndrom khronichnoi vtomy ta porushennia nespetsyfichnoho protyinfektsiinoho zakhystu. Bukovynskyi medychnyi visnyk. 2013;17(1):115-9.

34. Robustillo-Villarino M., Alegre-Sancho J.J., Rodilla-Sala E, Corrales A, Llorca J, Gonzalez-Gay MA, et al. Pulse wave velocity and augmentation index are not independently associated with carotid atherosclerosis in patients with rheumatoid arthritis. Clin. Rheumatol. 2017 Nov; 36(11):2601-2606.

35. Berezhnyi VV, Romankevych IV. Yuvenilnyi revmatoidnyi artryt i ateroskleroz: novi pohliady na dva zakhvoriuvannia. Sovremennaia pedyatryia. 2011;5(39):126-9.

36. Wevers-de Boer K, Visser K, Heimans L, Ronday HK, Molenaar E, Groenendael JH, et al. Remission induction therapy with methotrexate and prednisone in patients with early rheumatoid and undifferentiated arthritis (the IMPROVED study). Ann Rheum Dis. 2012 Sep;71(9):1472-7. doi: 10.1136/annrheumdis-2011-200736.

37. Flammer AJ, Sudano I, Hermann F, Gay S, Forster A, Neidhart M, et al. Angiotensin-converting enzyme inhibition improves vascular function in rheumatoid arthritis. Circulation. 2008 Apr 29;117(17):2262-9. doi: 10.1161/CIRCULATIONAHA.107.734384.

38. Svintsytskyi AS. Revmatoidnyi artryt: vchora, sohodni, zavtra [Internet]. Zdorovia Ukrainy. 2015 [tsytovano 2017 Ser 16]. Dostupno: http://health-ua.com/article/17377-revmatodnij-artrit-vchora-sogodn-zavtra.

39. First Latin American position paper on the pharmacological treatment of rheumatoid arthritis. By the Latin American Rheumatology Associations of the Pan American League of Associations for Rheumatology (PANLAR) and the Grupo Latinoamericano de Estudio de Artritis Reumatoide (GLADAR). Rheumatology. 2006;45:117-22.

40. Hafstrom I, Rohani M, Deneberg S, Wörnert M, Jogestrand T, Frostegård J. Effects of Low-dose prednisolone on endothelial function, atherosclerosis, and traditional risk factors for atherosclerosis in patients with rheumatoid arthritis - A randomized study. J Rheumatol. 2007 Sep;34(9):1810-6.

41. Lindhardsen J, Gislason GH, Jacobsen S, Ahlehoff O, Olsen AMS, Madsen OR et al. Non-steroidal anti-inflammatory drugs and risk of cardiovascular disease in patients with rheumatoid arthritis: a nationwide cohort study. Ann Rheum Dis. 2014 Aug;73(8):1515-1521. doi: 10.1136/annrheumdis-2012-203137.

42. del Rincón I, Polak JF, O'Leary DH, Battafarano DF, Erikson JM, Restrepo JF, et al. Systemic inflammation and cardiovascular risk factors predict rapid progression of atherosclerosis in rheumatoid arthritis. Ann Rheum Dis. 2015 Jun;74(6):1118-23. doi: 10.1136/annrheumdis-2013-205058.

43. Rudiuk LI. Osoblyvosti likuvannia arterialnoi hipertenzii pry revmatoidnomu artryti. Ukrainskyi revmatolohichnyi zhurnal. 2012;48(2):53-5.