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Georgiana Iftimie
Clinical Emergency Hospital of Bucharest, Bucharest, Romania

Ana Maria Alexandra Stanescu
Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

Mihaela A. Iancu
Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

Anca Pantea Stoian
Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

Razvan Hainarosie
Carol Davila University of Medicine and Pharmacy, Prof. Dr. D. Hociota Institute of Phonoaudiology and Functional ENT Surgery, Bucharest, Romania

See next page for additional authors

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Authors
Georgiana Iftimie, Ana Maria Alexandra Stanescu, Mihaela A. Iancu, Anca Pantea Stoian, Razvan Hainarosie, Bogdan Socea, Gheorghita Isvoranu, Dragos Marcu, Tiberiu P. Neagu, and Camelia C. Diaconu

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Review

The importance of early arthritis in patients with rheumatoid arthritis

Georgiana Iftimie[1], Ana Maria Alexandra Stănescu[2], Mihaela Adela Iancu[2], Anca Pantea Stoian[2], Răzvan Hainăroșie[2,3], Bogdan Socea[2,4], Gheorghița Isvoranu[5], Dragoș Marcu[2,6], Tiberiu Paul Neagu[1,2], Camelia C. Diaconu[1,2]

[1]Clinical Emergency Hospital of Bucharest, Bucharest, Romania
[2]Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[3]Prof. Dr. D. Hociota Institute of Phonoaudiology and Functional ENT Surgery, Bucharest, Romania
[4]St. Pantelimon Emergency Hospital, Department of surgery, Bucharest, Romania
[5]Victor Babes National Institute of Pathology, Bucharest, Romania
[6]Emergency University Central Military Hospital, Bucharest, Romania

Abstract

Rheumatoid arthritis (RA) is a systemic inflammatory disorder that manifests predominantly in the synovial joint, where it causes a chronic inflammatory process, leading to early osteoarticular destructions. These destructions are progressive and irreversible, generating a significant functional deficiency. During the last years, the diagnostic approach of RA has focused on early arthritis. Early arthritis can develop into established RA or another established arthropathy, like systemic lupus erythematosus or psoriatic arthritis. It can have a spontaneous resolution or may remain undifferentiated for indefinite periods of time.

The management of early arthritis has changed considerably in the past few years, under the influence of new concepts of diagnosis and new effective therapies. The treatment goal of early arthritis should now be the clinical remission and prevention of joint destruction. Methotrexate is the first line of therapy, used to treat early arthralgia and to reverse or limit impending exacerbation to RA. Biological treatment is used as a second line therapy in patients with severe disease who do not respond or have a contraindication to disease-modifying antirheumatic drugs (DMARDs). Patients with early arthritis should usually be identified and directed to rheumatologists to confirm the presence of arthritis, and to establish the correct diagnosis plus to initiate the proper treatment strategies.

Keywords : early arthritis, rheumatoid arthritis, DMARDs, anticarbamilated protein antibodies.

Highlights

- ✓ Patients with early arthritis should be referred to the rheumatologist, to be able to establish a fast diagnosis and prompt therapy.
- ✓ The management of early arthritis should include not only drug treatment but also specific medical education.

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*Corresponding author: Camelia Diaconu, Carol Davila University/ Clinical Emergency Hospital of Bucharest, Romania
E-mail: drcameliadiaconu@gmail.com

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disorder that manifests predominantly in the synovial joint, where it causes a chronic inflammatory process, leading to osteoarticular destructions. These destructions occur early and are progressive and irreversible, generating a significant functional deficiency. RA is frequently accompanied by significant and varied systemic manifestations and could reduce life expectancy due to several complications.

RA is the most common inflammatory rheumatic illness. The articular and systemic consequences have a significant impact on patients' quality of life and prognosis, but also on the healthcare systems. The disease has considerable heterogeneity and can have different forms: mild, non-erosive, sometimes with spontaneous remission, or severe, rapidly progressive forms, with significant and irreversible osteoarticular destructions.

For a better prognosis of patients with RA, establishing an earlier diagnosis and initiating treatment is critical. In clinical practice, diagnosis of early arthritis has become an important step. During the last years, the diagnostic approach of RA is focused on early arthritis.

Inflammatory arthritis is one of the most common pathological findings in clinical rheumatology. Identifying the main disease can be very difficult, especially in an early stage. In clinical practice, an early inflammatory arthritis is often undifferentiated (1). Early arthritis can often lead to established RA or other arthropathies, such as systemic lupus erythematosus or psoriatic arthritis.

Most of the symptoms in early arthritis remain undifferentiated for indefinite periods of time. For a better evaluation of the diagnosis of arthritis, recognizing the inflammatory arthritis is necessary. The next step is to search for a definite diagnosis and to estimate the risk of developing persistent arthritis. An optimal therapeutic strategy is essential (2, 3). Although the prognosis of early arthritis is still difficult to assess, a combination of clinical, laboratory, and radiological findings may help to predict patients' outcomes.

Discussions

Etiology

Numerous factors influence the onset of RA, the majority being common with those involved in the appearance of early arthritis. The exact cause of the RA is unknown; it is considered a disease with multifactorial complex determinism (4). It can have multiple risk factors involving the host organism (e.g. genetic, hormonal factors), environmental factors (smoking, infections - Porphyromonas gingivalis, Ebstein Barr virus, Mycoplasma pneumoniae), obesity, or socio-economic status (5).

The evolutive phases of rheumatoid arthritis are influenced by the presence of the risk factors: genetics (HLA-DRB1, PTPN22, STAT4, PAD14), smoking or bacteria like Porfiromonas gingivalis or Porfiromonas copri (6).

These factors can precede the pre-clinical rheumatoid arthritis phase (no symptoms), which involves the systemic autoimmunity, with high levels of rheumatoid factor, proinflammatory cytokines, high sensitive C-reactive protein (CRP), and the positivity of anti-citrullinated protein antibodies (ACPA) and anti-protein carbamylated antibodies (7).

Clinical manifestations

The early rheumatoid arthritis phase involves nonspecific signs and symptoms, including articular ones. The definite rheumatoid arthritis phase fulfills the classification criteria, with systematic and articular manifestations, high inflammatory markers such as C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), high rheumatoid factor, and positive anti-citrullinated protein antibodies (ACPA) (8).

The diagnosis is based on the European League Against Rheumatism (EULAR) defined characteristics, patients with arthralgia being at risk for RA (9). These parameters are used in patients with arthralgia without clinical arthritis and without other diagnosis or other explanation for the arthralgia. The diagnosis of RA involves a history of joint symptoms with recent onset (duration less than 1 year) (10); symptoms localized in metacarpo-phalangeal joints; duration of morning stiffness more than 60 minutes; most severe symptoms present more in the early morning than the rest of the day; presence of a first degree relative with RA; first movement difficulties; and positive squeeze test of metacarpophalangeal joints (11).

The undefined arthritis is approached differently by two important rheumatology groups' associations: the Norfolk group defines it as two or more swollen joints, for no less than two weeks, and the Leiden group sees it as one or more swollen joints, diagnosed by a rheumatologist, that have no other cause (12, 13).

Regarding the symptoms, there is a series of nonspecific symptoms, like fatigue, undefined illness, nonspecific muscular pain, mood disorders, or sub fever. The articular symptoms include stiffness with variable duration, non-characteristic to inflammatory pain, nonspecific joint pain, symptoms of palindromic

rheumatism and dysfunctional symptoms that can affect the daily activities (14).

The connective-diseases screening questionnaire and the rheumatoid arthritis questionnaire have high specificity and sensibility. In a retrospective meta-analysis that included studies published between 1940-2012, using as inclusion criteria the symptoms of RA at the onset of the disease, the authors have found that the most frequent symptoms were joint swelling, local pain and sensitivity, joint fatigue, fatigability, and asthenia, all symptoms having an emotional impact (15).

Paraclinical diagnosis

Paraclinical diagnosis is based on laboratory tests and imaging characteristics. Although there are no specific biological markers or certain imaging tests for early arthritis, because studies are still ongoing, most of them are common for RA and early arthritis. The same meta-analysis cited previously found positivity of anti-citrullinated protein antibodies (ACPA) before rheumatoid factor (FR) titers increased at a shorter interval before diagnosis, a positive titer of anti-citrullinated protein antibodies (ACPA), alpha tumor necrosis factor (TNF alpha), interleukins 1,2 and 15 (IL 1, IL2, IL 15), and gamma interferon (15).

A brief report showed the presence of anticarbamilated protein antibodies (anti-CarP) and their role in predicting the development of RA (16). These are relatively new antibodies, studies showing that 16% of patients with RA have anti-CarP IgG even in the absence of anti-citrullinated protein antibodies (ACPA). They are associated with a severe destructive disease at the articular level; they can be detected up to 4 years prior to RA (16).

The anti-ribonucleoprotein A2/ anti RA22 nuclear heterologous antibodies are present in 20-30% of patients diagnosed with AR, but also in systemic lupus erythematosus (SLE) or juvenile idiopathic arthritis (JIA) (17). The epitope recognition is different in RA patients, the specificity for RA is approximately 90%; it is not associated with radiological progression. Serum level equals the disease activity, with the tendency to normalize during remission.

Imaging in early arthritis

Imaging has a very important role in the diagnosis of RA. However, in early arthritis, imaging may not be as useful as the clinical examination, due to the features that tend to appear late, especially at ultrasonography. Imaging is important in order to confirm the further installation of RA.

Ultrasonography (US): A study combining routine assessment and power Doppler ultrasonography was performed in order to predict the progression to RA from early-onset undifferentiated arthritis (18). The study involved 149 patients with undifferentiated arthritis, with early onset <16 weeks. The examined joints were radiocarpal, metacarpophalangeal joints 2-5, and interphalangeal joints 2-5 bilateral. The results showed that the power Doppler signal present at more than 3 joints increases the probability of progression to AR to 41% and the positivity of anti-citrullinated protein antibodies (ACPA) or rheumatoid factor increases the probability to 65% (19).

Magnetic resonance imaging (MRI): In early arthritis, we can use RAMRIS (Rheumatoid Arthritis MRI Score) to observe the synovitis, erosion and bone edema. Synovitis of interphalangeal joints is an independent predictor for RA, with high relative risk. Bone edema of metacarpo-phalangeal and radiocarpal could be independent predictors (20).

Treatment of early arthritis

The management of an early arthritis has changed substantially in the past few years as the result of new concepts proposed for diagnosis and new effective therapies. The treatment goal of such early arthritis should now be represented by clinical remission and prevention of joint destruction. The 2016 update of the European League Against Rheumatism (EULAR) recommendations for the management of early arthritis (March 2017) includes 3 general principles and 12 recommendations (21).

Principles:

- The first principle indicates that the decisions taken in the management of the disease should be based on the relationship between patients and rheumatologist.
- The second principle highly recommends that rheumatologists be the first specialists to examine the patient with early arthritis.
- The third principle highlights the steps to the definitive diagnosis of early arthritis that should be made only after a full history and clinical examination and that should guide the laboratory analysis and additional investigations.

Recommendations

- Recommendation 1 strongly advises that the patient be seen early and examined by a rheumatologist, no later than 6 weeks after joints symptoms appear.
- Recommendation 2 places clinical examination first, with the condition of confirmation by ultrasonography.
- Recommendation 3 indicates a series of parameters, as the number of painful and swollen joints, the level of acute phase reactants, the rheumatoid factor or anti-citrullinated protein antibodies titer, and the imaging

changes, that must be evaluated in patients with undifferentiated early arthritis.

- Recommendation 4 strongly indicates that treatment with disease-modifying antirheumatic drugs (DMARDs) should start no later than 3 months after the joint symptoms appear, even if patients do not fulfill the classification criteria for a rheumatologic inflammatory disease.
- Recommendation 5 highlights that methotrexate should be used as first line therapy in patients at risk for persistent disease with no contraindication for MTX.
- Recommendation 6 strongly recommends nonsteroidal anti-inflammatory drugs (NSAIDs) as a therapy that should be used carefully, only for a short period of time and at the lowest effective dose.
- Recommendation 7 presents the beneficial effects of corticosteroids on pain, swelling, and structural progression reduction, but recommend corticosteroids only as a temporary adjuvant treatment, no longer than 6 months.
- Recommendation 8 advises taking into account the comorbidities and the side effects of disease-modifying antirheumatic drugs (DMARDs) in the therapeutic management of early arthritis.
- Recommendation 9 indicates some variables, including assessments of the number of swollen and painful joints, visual analog scale (VAS), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), be used in monitoring the disease activity, and that these should be performed between 1 and 3 months until reaching the therapeutic target.
- Recommendation 10 takes into consideration rehabilitation exercises and therapies that could be used as adjuvants for treatment.
- Recommendation 11 highly recommends primary prevention in patients with early arthritis, including quitting smoking, dental care, weight control, or vaccination.
- Recommendation 12 highlight the importance that different information and education programs could have on patients in order to help them maintain work capacity and to cope with the pain and the functional deficit.

Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), if used long term, is a major risk factor for renal injury, via direct nephrotoxic effects, with acute tubular necrosis. Kidney injury may lead to chronic kidney disease, with the necessity of chronic dialysis (22, 23). The renal function may be affected also by other mechanisms, such as obstruction of the urinary tract, which may manifest over time with chronic kidney disease, usually well tolerated by the patients, due to slow installation (24, 25). Use of NSAIDs as analgesics in the postoperative period, for example, may further deteriorate the renal function (26-28). Treatment with NSAIDSs should be used with caution in patients with cardiovascular comorbidities (29, 30).

Disease-modifying antirheumatic drugs (DMARDs) treatment

The conventional anti-rheumatic drugs (synthetic disease-modifying/ csDMARDs) have been shown to diminish disease progression in chronic inflammatory arthritis, such as RA and psoriatic arthritis (PsA) (31). Furthermore, biological DMARDs have demonstrated rapid and sustained disease control associated with a reduction of joint destruction.

Methotrexate (MTX) is the first line therapy used to treat early arthralgia, to reverse or limit impending exacerbation to RA (32). A randomized, placebo-controlled study (2015) was done in patients with no ACPA/ FR, without clinical arthritis, arthralgia <1 year (suspected clinical arthralgia), MRI inflammation, treated with 120 mg methylprednisolone + MTX / placebo for 12 months (33). Results showed an important influence of the treatment on the installation of clinical arthritis (33).

A prospective, placebo-controlled, double-blind study (2012) in 110 patients with undifferentiated arthritis using MTX 15 mg/ week, for 1 year showed the improvement and reduction of the progression of arthralgia, especially in ACPA positive patients (34).

Corticosteroid treatment. Corticosteroids improve clinical and radiological outcomes. Therapy with systemic corticosteroids should be temporary due to the risk of side effects, including weight gain, hypertension, diabetes, cataract, and osteoporosis, which justify careful monitoring and appropriate prevention (35). Dexamethasone has demonstrated effect on autoantibody levels in early arthritis (36). In 2010, in a case-control study on 83 ACPA positive patients with arthralgia, without signs of undifferentiated arthritis, using 2 administrations of Dexamethasone 100 mg at 6-week intervals, the results showed ACPA and FR titration reduction, but no delay in the progression of the disease to clinically non-differentiated arthritis (37).

Antimalarial treatment. Although the current data could not show an important effect of hydroxychloroquine (HCQ) in early arthritis or RA, as it has in systemic lupus erythematosus (SLE), some studies have established its possible use in specific patients.

Hydroxychloroquine. It seems that the antimalarial therapy can be used in case of arthritis progressing to RA or other connective tissue diseases in patients with palindromic rheumatism. In a retrospective study on 113 patients diagnosed with palindromic rheumatism and 33 with RA, this therapy reduced progression to RA in 69% of patients treated with HCQ (38, 39).

Biological treatment. This kind of treatment opened a new era in the management of many inflammatory diseases. In early arthritis and RA, it is used as a second line therapy in patients with severe disease who do not respond or who have a contraindication to DMARDs, the first line of therapy still remaining the methotrexate.

Rituximab. The PRAIRI study (2016) showed the prevention of RA by B cell-directed therapy in the earliest phase of the disease. In this randomized, placebo-controlled, double-blind study, on 81 patients during 29 months, without clinically obvious arthritis, with rheumatoid factor, ACPA positive, elevated levels of C-reactive protein, subclinical US/ MRI synovitis, with 40 patients using 1000 mg rituximab/ 40 placebo (premedication with 100 mg methylprednisolone), results showed that patients using rituximab developed RA at 24 months vs 12 months with placebo (40).

Infliximab did not demonstrate surprising results. In a double-blind, placebo-controlled study on 17 patients with undifferentiated arthritis <12 months (10 using infliximab, 7 placebo), this treatment showed a C-reactive protein reduction after 14 weeks, with HAQ (Health Assessment Questionnaire) improvement (40). In the 26th week: no statistical significance DAS 28 (Disease Activity Score), with only a small reduction in morning stiffness. In week 52, all patients (Interferon users+ placebo) had developed RA.

Abatacept. Studies using this biological treatment are yet in progress. The APPIPRA study aims to show the reverse of subclinical inflammation. Begun in December 2017 and estimated to finish in December 2018, this study uses a randomized, placebo-controlled design on anti-citrullinated protein antibodies (ACPA) positive patients with joint pain, without clinically obvious arthritis, comparing 125 mg Abatacept vs placebo (41, 42).

Conclusions

Patients with early arthritis should be referred to the rheumatologist in order to recognize the presence of arthritis and to confirm the potential diagnosis. Prompt initiation of treatment is essential. The management of early arthritis should include drug treatment associated with medical education (43). Comorbidities in patients with early arthritis play an important role for the therapeutical decision (44-46). The shared decision between patient and rheumatologist plays an important role for allied healthcare professionals.

Though no cure for rheumatoid arthritis is available, patients can take positive steps to delay some of the more severe joints damage and allow them to continue to live a long, healthy life.

Conflict of interest disclosure

The authors declare that there are no conflicts of interest to be disclosed for this article.

References

1. Machado P, Castrejon I, Katchamart W, et al. Multinational evidence-based recommendations on how to investigate and follow-up undifferentiated peripheral inflammatory arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis*. 2011; 70(1): 15–24. PMID: 20724311, DOI: 10.1136/ard.2010.130625
2. Huizinga TWJ, Machold KP, Breedveld FC, Lipsky PE, Smolen JS. Criteria for early rheumatoid arthritis: from Bayes' law revisited to new thoughts on pathogenesis. *Arthritis Rheum*. 2002; 46(5): 1155–9. PMID: 12115216, DOI: 10.1002/art.10195
3. Combe B. Early rheumatoid arthritis: strategies for prevention and management. *Best Pract Res Clin Rheumatol*. 2007; 21(1): 27–42. PMID: 17350542, DOI: 10.1016/j.berh.2006.08.011
4. Klareskog L, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, Ronnelid J, Haris HE, Ulfgren AK, Rantapaa-Dahlqvist S, Eklund A, Padyukov L, Alfredsson L. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-Dr (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum*. 2006; 54(1): 38–46. PMID: 16385494, DOI: 10.1002/art.21575
5. Viatte S, Plant D, Bowes J, Lunt M, Eyre S, Barton A, Worthington J. Genetic markers of rheumatoid arthritis susceptibility in anti-citrullinated peptide antibody negative patients. *Ann Rheum Dis*. 2012; 71(12): 1984–90. PMID: 22661644, DOI: 10.1136/annrheumdis-2011-201225
6. Yarwood A, Huizinga TW, Worthington J. The genetics of rheumatoid arthritis: risk and protection in different stages of the evolution of rheumatoid arthritis. *Rheumatology*. 2016;

55(2): 199–209. PMID: 25239882, DOI: 10.1093/rheumatology/keu323

7. Padyukov L, Seielstad M, OngRT, Ding B, Ronnelid J, Seddighzadeh M, Alfredsson L, Klareskog L. A genome-wide association study suggests contrasting associations in ACpA-positive versus ACpA-negative rheumatoid arthritis. *Ann Rheum Dis*. 2011; 70(2): 259–6. PMID: 21156761, DOI: 10.1136/ard.2009.126821
8. Van Steenbergen HW, Aletaha D, Beaart-van de Voorde LJ, et al. EULAR definition of arthralgia suspicious for progression to rheumatoid arthritis. *Ann Rheum Dis*. 2017; 76(3): 491-6. PMID: 27991858, DOI: 10.1136/annrheumdis-2016-209846
9. Van Steenbergen HW, van Nies JA, Huizinga TW, Bloem JL, Reijnierse M, van der Helm-van Mil AH. Characterising arthralgia in the preclinical phase of rheumatoid arthritis. *Ann Rheum Dis*. 2015; 74(6): 1225–32. PMID: 24718962, DOI: 10.1136/annrheumdis-2014-205522
10. Iftimie G, Bratu OG, Socea B, Iancu MA, Stanescu AMA, Dediu G. Paraschiv B, Diaconu C. Pulmonary involvement in rheumatoid arthritis – another face of the coin. *Arch Balk Med Union*. 2018; 53(1): 89-95.
11. Stack RJ, Van Tuyl LH, Sloots M, van de Stadt LA, Hoogland W, Maat B, Mallen CD, Tiwana R, Raza K, van Schaardenburg D. Symptom complexes in patients with seropositive arthralgia and in patients newly diagnosed with rheumatoid arthritis: a qualitative exploration of symptom development. *Rheumatology*. 2014; 53(9): 1646–53. PMID: 24729397, DOI: 10.1093/rheumatology/keu159
12. Machado P, Castrejon I, Katchamart W, et al. Multinational evidence-based recommendations on how to investigate and follow-up undifferentiated peripheral inflammatory arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis*. 2011; 70(1): 15–24. PMID: 20724311, DOI: 10.1136/ard.2010.130625
13. Combe B, Landewe R, Lukas C, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis*. 2017; 66(1): 34–45. PMID: 16396980, DOI: 10.1136/ard.2005.044354
14. Van der Linden MP, le Cessie S, Raza K, van der Woude D, Knevel R, Huizinga TW, van der Helm-van Mil AH. Long-term impact of delay in assessment of patients with early arthritis. *Arthritis Rheum*. 2010; 62(12): 3537–46. PMID: 20722031, DOI: 10.1002/art.27692
15. Bacconnier L, Rincheval N, Flipo R-M, et al. Psychological distress over time in early rheumatoid arthritis: results from a longitudinal study in an early arthritis cohort. *Rheumatology*. 2015; 54(3): 520–7. PMID: 25224416, DOI: 10.1093/rheumatology/keu371
16. van den Broek M, Dirven L, Klarenbeek NB, Molenaar TH, Han KH, Kerstens PJ, Huizinga TW, Dijkmans BA, Allaart CF. The association of treatment response and joint damage with ACPA-status in recent-onset RA: a subanalysis of the 8-year follow-up of the BEST study. *Ann Rheum Dis*. 2012; 71(2): 245–8. PMID: 22110122, DOI: 10.1136/annrheumdis-2011-200379
17. Degboé Y, Constantin A, Nigon D, et al. Predictive value of autoantibodies from anti-CCP2, anti-MCV and anti-human citrullinated fibrinogen tests, in early rheumatoid arthritis patients with rapid radiographic progression at 1 year: results from the ESPOIR cohort. *RMD Open*. 2015; 1(1): e000180. PMID: 26635969, DOI: 10.1136/rmdopen-2015-000180
18. Rezaei H, Torp-Pedersen S,af Klint E, Backheden M, Kisten Y, Gyori N, van Vollenhoven RF. Diagnostic utility of musculoskeletal ultrasound in patients with suspected arthritis—a probabilistic approach. *Arthritis Res Ther*. 2014; 16(5): 448. PMID: 25270355, DOI: 10.1186/s13075-014-0448-6
19. Sahbudin I, Pickup L, Cader Z, Abishek A, Buckley CD, Allen G, Nightingale P, de Pablo P, Raza K, Filer A. Ultrasound-defined tenosynovitis is a strong predictor of early rheumatoid arthritis. *Ann Rheum Dis*. 2015; 74(Suppl2): 69–70.
20. Duer-Jensen A, Horslev-Petersen K, Hetland ML,Bak L, Ejberg BJ, Hansen MS, Johansen JS, Lindegaard HM, Vinterberg H, Moller JM, Ostergaard M. Bone edema on magnetic resonance imaging is an independent predictor of rheumatoid arthritis development in patients with early undifferentiated arthritis. *Arthritis Rheum*. 2011; 63(8): 2192–202. PMID: 21484772, DOI: 10.1002/art.30396
21. Combe B, Landewe R, Daiene CI, et al. 2016 update of the EULAR recommendations for the management of early arthritis. *Ann Rheum Dis*. 2017; 76(6): 948-959. PMID: 27979873, DOI: 10.1136/annrheumdis-2016-210602

22. Radulescu D, Stroescu AB, Pricop C, et al. Vitamin K influence on cardiovascular mortality in chronic hemodialysed patients. *Revista de Chimie*. 2017; 68(1): 52-54.
23. Niculae A, Peride I, Vinereanu V, et al. Nephrotic syndrome secondary to amyloidosis in a patient with monoclonal gammopathy with renal significance (MGRS). *Rom J Morphol Embryol*. 2017; 58(3): 1065-1068.
24. Bratu O, Mischianu D, Spanu D, et al. Paraneoplastic syndrome in primitive retroperitoneal tumours. *Chirurgia*. 2013; 108(1): 26-31.
25. Radavoi GD, Pricop C, Jinga V, et al. A comprehensive analysis of genome-wide association studies to identify prostate cancer susceptibility loci for the Romanian population. *Rom J Morphol Embryol*. 2016; 57(2): 467-475.
26. Stanimir M, Chiutu LC, Wese S, et al. Mullerianosis of the urinary bladder: a rare case report and review of the literature. *Rom J Morphol Embryol*. 2016; 57(2 Supplement): 849-852.
27. Constantinoiu S, Bârlă R, Iosif C, Cociu L, Gîndea C, Hoară P, Bratu O, Ruşitoru L. Difficulties in diagnosis and surgical treatment of a giant retroperitoneal lipoma. *Chirurgia (Bucur)*. 2009; 104(3): 363-7.
28. Scarneciu I, Lupu S, Pricop C, et al. Morbidity and impact on quality of life in patients with indwelling ureteral stents: A 10-year clinical experience. *Pakistan Journal of Medical Sciences*. 2015; 31(3): 522-6. PMID: 26150836, DOI: 10.12669/pjms.313.6759
29. Diaconu CC, Manea M, Iancu MA, Stanescu AMA, Socea B, Spinu DA, Marcu D, Bratu OG. Hyponatremia in patients with heart failure: a prognostic marker. *Revista de Chimie*. 2018; 69(5): 1071-1074.
30. Diaconu CC, Dragoi CM, Bratu OG, Neagu TP, Pantea Stoian A, Cobelschi PC, Nicolae AC, Iancu MA, Hainarosie R, Stanescu AMA, Socea B. New approaches and perspectives for the pharmacological treatment of arterial hypertension. *Farmacia*. 2018; 66(3): 408-415.
31. Ramiro S, Gaujoux-Viala C, Nam JL, Smolen JS, Buch M, Gossec L, van der Heijde D, Winthrop K, Landewe R. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis*. 2014; 73(3): 529–35. PMID: 24401994, DOI: 10.1136/annrheumdis-2013-204575
32. Ramiro S, Smolen JS, Landewé R, van der Heijde D, Dougados M, Emery P, de Wit M, Cutolo M, Oliver S, Gossec L. Pharmacological treatment of psoriatic arthritis: a systematic literature review for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis*. 2016; 75(3): 490–8. PMID: 26660203, DOI: 10.1136/annrheumdis-2015-208466
33. Visser K, Katchamart W, Loza E, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis*. 2009; 68(7): 1086–93. PMID: 19033291, DOI: 10.1136/ard.2008.094474
34. Dixon WG, Abrahamowicz M, Beauchamp M-E, Ray DW, Bernatsky S, Suissa S, Sylvestre MP. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. *Ann Rheum Dis*. 2012; 71(7): 1128–33. PMID: 22241902, DOI: 10.1136/annrheumdis-2011-200702
35. Paunica M, Gheorghiu R, Curaj A, Holeab C. Foresight for restructuring R&D systems. *Amfiteatru Economic*. 2009; 11(25): 201-210.
36. Sydorchuk LP, Bukach OP, Fediv OI, Sydorchuk AR, Petrynych OA, Kazantceva TV, Melnychuk LV, Nikyfor IV, Semianiv MM, Repchuk YV, Sheremet MI, Sydorchuk RI, Yarynych YM, Korovenkova OM, Boyko VV. Cytokines cascade changes in patients with rheumatoid arthritis depending on endothelial NO-synthase (T-786C) genes polymorphism. *Arch Balk Med Union*. 2017, 52(1): 32-38.
37. Katz SJ, Russell AS. Re-evaluation of antimalarials in treating rheumatic diseases: re-appreciation and insights into new mechanisms of action. *Curr Opin Rheumatol*. 2011; 23(3): 278–81. PMID: 21448012, DOI: 10.1097/BOR.0b013e32834456bf
38. Scarneciu I, Muntean I, Scarneciu C, et al. Diagnosis and renal lithiasis treatment using ultrasounds. *Metalurgia International*. 2010; 15(11): 112-115.
39. Listing J, Kekow J, Manger B, Burmester GR, Pattloch D, Zink A, Strangfeld A. Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab. *Ann Rheum Dis*. 2015; 74(2): 415–21. PMID: 24291654, DOI: 10.1136/annrheumdis-2013-204021

40. Klarenbeek NB, Güler-Yüksel M, van der Heijde DM, Hulsmans HM, Kerstens PJ, Molenaar TH, de Sonnaville PB, Huizinga TW, Dijkmans BA, Allaart CF. Clinical synovitis in a particular joint is associated with progression of erosions and joint space narrowing in that same joint, but not in patients initially treated with infliximab. *Ann Rheum Dis*. 2010; 69(12): 2107–13. PMID: 20610442, DOI: 10.1136/ard.2010.131201
41. Avci AB, Feist E, Burmester G-R. Biologicals in rheumatoid arthritis: current and future. *RMD Open*. 2015; 1(1): e000127. PMID: 26535144, DOI: 10.1136/rmdopen-2015-000127
42. Pandi E, Maxim LS, Cristian A, et al. Acute Urinary Retention due to a Prostatic Cystadenoma: A Case Report. *Urology Journal*. 2016; 13(4): 2797-2799. PMID: 27576889
43. Dediu G, Crîşmaru I, Bajan M, Ionescu G, Ilie M, Udrea G, Diaconu C, Bartoş D. The non-pharmacologic treatment of rheumatoid arthritis. *Revista Română de Reumatologie*. 2015; 24(2): 61-65.
44. Diaconu CC, Dediu GN, Iancu MA. Drug-induced arterial hypertension, a frequently ignored cause of secondary hypertension: a review. *Acta Cardiologica*. 2018; 1: 1-7. PMID: 29291681, DOI 10.1080/00015385.2017.1421445.
45. Diaconu C, Bălăceanu A, Moroşan E. Sepsis biomarkers: past, present and future. *Farmacia*. 2015; 63(6): 811-5.
46. Ciuhu AN, Rahnea Nita RA, Popescu M, Badiu CD, Pantea Stoian AM, Lupuliasa D, Gherghiceanu F, Diaconu CC. Evidence of strong opioid therapy for palliation of breathlesness in cancer patients. *Farmacia*. 2017; 65(2): 173-178.