24. Насонов Е.Л. Автоиммунные ревматические заболевания: итоги и перспективы научных исследований. Е.Л. Насонов, Е.Н. Александрова, А.А. Навиков. Научно-практическая ревматология. 2015;53, Но 3: 230-237.
25. Насонов Е.Л. Т-регуляторные клетки при ревматоидном артрите/ Е.Л. Насонов(и др). научно-практическая ревматология. 2014;52(4):430-437.
26. Насонов Е.Л. Достижения ревматологии в XX1 в. Е.Л. Насонов. Научно - практическая ревматология. 2014;52(2): 133-141.
27. Новиков Л.А., Александрова Е.Н., Диатропова М.А. Роль цитокинов в патогенезе ревматоидного артрита. Научно - практическая ревматология 2010; 2: 71-82
28. Соболева Е.М. Ювенильный ревматоидный артрит: современное состояние проблемы (обзор литературы). Вестник физиотерапии и курортологии.
29. Федеральные клинические рекомендации оказанию медицинской помощи детям с юношеским артритом с системным началом. Под ред. А.А. Баранова. М., 2009:44.
30. Федеральные клинические рекомендации по оказанию медицинской помощи детям с юношеским артритом с системным началом. Под ред. А.А. Баранова. М., 2015: 24.
31. Федоров Е.С. Роль цитокиновой сети в регуляции воспаления при различных вариантах ювенильного артрита. Е.С. Федоров, С.О. Салугина, Н.Н. Кузьмина. Научно-практическая ревматология. 2009;3:74-89.
32. Хаитов Р.М. Игнатьева Г.А., Сидорович И.Г. Иммунология. И. Медицина, 2000.
33. Харитонова Л.А., Соболева Н.Г. Роль инфекционного фактора при ювенильном ревматоидном артрите у детей. Харитонова Л.А., Соболева Н.Г. Российский вестник перинатологии и педиатрии. 2018, 63(3),59-63с.
34. Чернишова О.Е., Конюшевская А.А., Вайзер Н.В. Ювенильный ревматоидный артрит: этиология, патогенез. Травма, Том 19, №2, 2018:99-105.
35. Ювенильный артрит: клинические рекомендации для педиатров. Детская ревматология/Под редакцией А.А.Баранова, Е.И.Алексеевой.-М.: Педиатръ, 2013:120.
36. Classidy J.T. Textbook of pediatric rheumatology. - 6th ed./ J.T. Cassidy (et al.) - Philadelphia: Saunders Elsevier, 2010:794.
37. De Benedetti F. Inflammatory cytokines in the phathogenesis and treatment of systemic juvenile idiophatic arthritis. De Benedetti F. Pediatric Rheumatology Online J. 2005;3:122-136.
38. Feldmann M. Role of cytokines in rheumatoid arthridis: an education in pathophysiology and therapeutics. M. Feldmann, S. Maini. Immunological Reviews. 2008;223:7-19. De Benedetti F. Inflammatory cytokines in the phatogenesis and treatment of systemic juvenile idiopatic arthritis / De Benedetti F. Pediatric Rheumatology Online J. 2005;3:122-136.
39. Majka D.S. Holes V.M. Can We Accuratelly Pediatric the Development of Rheumatoid Arthritis in the Preclinical Phase Arthritis Rheum 2003; 48:2701-2705
40. Pascual V. Role of interleukin -1 (IL-1) in the pathogenesis of systemic onset juvenile idiopatic arthritis and clinical response to IL-1 blockade / V. Pascual [et al.]. J. Experimental Medicine. 2005;201:1479-1486.

Tulegenova G. M.

THE CONCEPT OF RHEUMATOID ARTHRITIS AND MODERN PRINCIPLES OF TREATMENT

Tashkent Pediatric Medical Institute

The article contains a review of the literature of foreign authors on the disease rheumatoid arthritis. The sources, summarizing the concepts of classification, authors systematized data from various literary etiology, classification, etiology, risk factors, pathogenesis, pathophysiology, course of the disease, as well as diagnosis and treatment. Rheumatoid arthritis, clinical picture, diagnosis, treatment.

Relevance. Rheumatoid arthritis (RA) is a chronic multisystem disease of unknown etiology. Although RA is characterized by a variety of systemic manifestations, its most typical feature is persistent, inflammatory synovitis, symmetrically affecting peripheral joints. A distinctive feature of RA is that synovitis leads to the destruction of articular cartilage and erosion of the underlying bone tissue with subsequent deformation of the joints. Despite the great destructive potential of this nosology, the course of the disease is highly variable.In some patients, this manifests itself only as mildly expressed oligoarthritis of a rather short duration with minimal damage to the joint(s), while in other patients there is a continuous progression of polyarthritis with the development of

severe joint deformation. In most patients, the disease has an undulating course. [1,4].

Etiology. In the development of rheumatoid arthritis, there are several factors (rheumatological triad): Genetic predisposition; Infectious factor; Triggering factors such as: intoxication, hypothermia, stress, hyperinsolation, endocrinopathy, mutagenic medications. [2] Risk factors. Gender. Women are more likely than men to develop rheumatoid arthritis; Age; Smoking; Environmental exposure; Obesity. People, especially women aged 55 years or younger, who are overweight or obese appear to have a slightly higher risk of developing rheumatoid arthritis [3,8].

Pathophysiology. The pathogenesis of RA is not fully understood. An external trigger (eg, cigarette smoking, infection, or trauma) that causes an autoimmune reaction leading to synovial hypertrophy and chronic joint inflammation, along with the possibility of extra-articular manifestations, is theorized to occur in genetically predisposed individuals. Synovial cell hyperplasia and endothelial cell activation are early events in the pathological process, which progresses to uncontrolled inflammation and subsequent destruction of cartilage and bone. Genetic factors and abnormalities of the immune system contribute to the spread of the disease.

CD4 T cells, mononuclear phagocytes, fibroblasts, osteoclasts, and neutrophils play major cellular roles in the pathophysiology of RA, while B cells produce autoantibodies (ie, rheumatoid factors). Abnormal production of a variety of cytokines, chemokines, and other inflammatory mediators has been demonstrated in patients with RA, including the following: tumor necrosis factor alpha (TNF-a): interleukin (IL)-1: IL-6: IL-8: transforming growth factor beta (TGF-B): fibroblast growth factor (FGF): platelet-derived growth factor (PDGF).

Ultimately, inflammation and overgrowth of the synovium (i.e., pannus) leads to the destruction of various tissues, including cartilage (bone, tendons, ligaments, and blood vessels. Although joint structures are the primary sites involved in RA, other tissues are also affected [5,6]/

Clinical manifestations. Start. It is characteristic that RA is a chronic polyarthritis. In approximately 65% of patients, the disease begins gradually with such general symptoms as fatigue, loss of appetite, general muscle weakness and intermittent pain in the musculoskeletal system, and only after this obvious signs of synovitis appear. These prodromal phenomena can persistently continue for weeks and months and seem to reject the diagnosis of RA. Symptoms characteristic of RA—symmetrical lesions of the joints of the hands, feet, wrists, and knees—appear gradually [9].

Signs and symptoms of joint damage. At first, pain, swelling and tenderness are vaguely localized in the joint area. The most common manifestation of established RA is pain in the affected joints, which increases with their movement. General stiffness of movement is often noted, especially after a period of immobility. Morning stiffness, lasting more than an hour, is a hallmark of inflammatory joint damage and serves as a differential diagnostic sign when trying to distinguish arthritis from arthrosis, a non-inflammatory joint damage.

Most patients also experience general symptoms such as weakness, fatigue, lack of appetite and weight loss. Although in some cases body temperature can rise to 40 ° C, values exceeding 38 ° C are considered unusual, which suggests an intercurrent illness (for example, infection. Large joints, such as the knee, feel hot to the touch, however Redness of the skin over the affected joint is rare.

Pain in an inflamed joint is associated primarily with the great pain sensitivity of the joint capsule, which is abundantly supplied with pain-sensitive nerve fibers that quickly respond to the slightest stretch or tension. Joint swelling is usually associated with the accumulation of synovial fluid in the joint cavity, hypertrophy of its synovial membrane and thickening of the joint capsule. [1,6].The spine is usually affected in the area of the joints of the upper cervical vertebrae. The lumbar spine, as a rule, is not involved in the pathological process, so pain in the lower back cannot be associated with RA. In some cases, synovitis and bursitis in the joints of the upper cervical vertebrae can lead to subluxation of the atlantoaxial joint. This usually manifests itself as pain in the occipital region and sometimes ends in compression of the spinal cord.

Extra-articular manifestations. RA is a systemic disease accompanied by various extra-articular manifestations. These extra-articular symptoms are very common, but not all of them are clinically significant. In some cases, they become the main witnesses to the activity of the disease and a source of disability for the patient and themselves require therapeutic measures. As a rule, these manifestations occur in individuals with high titers of rheumatoid factors.

Rheumatoid nodules develop in 20-30% of patients with RA. They are usually located in the periarticular tissues on the extensor surfaces or on surfaces subject to mechanical pressure, but can be localized in other areas, including the pleura and meningeal membranes. They are often found in the area of the olecranon bursa, in the proximal ulna, in the Achilles tendon and in the occipital region [1,5,3].

Rheumatoid vasculitis, which can affect any organ system, is found in patients with severe RA and high titers of circulating rheumatoid factor. In its most aggressive manifestations, rheumatoid vasculitis can cause polyneuropathy, multiple mononeuritis, ulceration and necrotization of the skin, gangrene of

the fingers, as well as certain visceral infarctions. Such common forms of vasculitis are, however, rare. Its more localized forms are more often observed, especially in representatives of the Caucasian race with high titers of rheumatoid factor. Rheumatoid vasculitis in the kidneys is rare [9,13].Lung and pleural lesions more commonly seen in men include pleurisy, interstitial fibrosis, pleuropulmonary rheumatoid nodules, pneumonitis, and arteritis. According to autopsy data, pleurisy in RA is very common, but rarely manifests itself symptomatically during life. In typical cases, pleural effusion contains very little glucose (unless it is infected). The complement content is also low, especially in comparison with that in the blood serum and when these determinations are correlated with the total amount of protein in the patient's blood serum. Pulmonary fibrosis causes impairment of the diffusion capacity of the lungs.Rheumatoid nodules can be single or located in small clusters. If they occur in patients with pneumoconiosis, Kaplan syndrome may develop - a diffuse nodular fibrotic process in the lungs. Sometimes rheumatoid nodules in the lungs undergo necrotization with the formation of a cavity, which can result in pneumothorax or bronchopleural fistula. [11,16,12].

Felty's syndrome can develop after inflammatory changes in the joints have reversed. Leukopenia is usually selective neutropenic in nature, with the number of polymorphonuclear leukocytes often being less than 1.5-1-10a/l. When examining the bone marrow, it is found to be moderately hypercellular with a paucity of mature neutrophils. However, the bone marrow may remain normal, hyperactive, hypoactive,

Drug therapy includes several classes of agents,

or blockade in the process of neutrophil maturation may be noted.

Laboratory tests. Erythrocyte sedimentation rate (ESR); C-reactive protein (CRP) level; Complete blood count (CBC); Rheumatoid factor (RF) test; Antinuclear antibody (ANA) test; Anticycliccitrullinated peptide (anti-citrullinated peptide) test CCP) and anti-mutant citrullinatedvimentin (anti-MCV) (currently used in the American College of Rheumatology [ACR]/European League Against Rheumatism [EULAR] classification criteria).

Treatment. Optimal care for patients with rheumatoid arthritis (RA) involves a multidisciplinary approach that includes both pharmacologic and nonpharmacologic treatments. Many non-pharmacological treatments are available for this disease, including exercise, diet, massage, counseling, stress reduction, physical therapy, and surgery. Surgical procedures used in the treatment of RA include the following: synovectomy, tenosynovectomy, tendon realignment, reconstructive surgery, or arthroplasty. arthrodesis.

including nonsteroidal anti-inflammatory drugs (NSAIDs), nonbiologic and biologic diseasemodifying antirheumatic drugs (DMARDs), immunosuppressants, and corticosteroids. In 2008, the American College of Rheumatology (ACR) developed guidelines and algorithms for the use of nonbiologic and biologic DMARDs for patients with RA [18]; an updated version was published in April 2012. Pharmacological treatments used include non-biological and biological DMARDs and adjuvant agents such as corticosteroids, NSAIDs and analgesics. AstudybyCallhoffetal.

Showed that biological agents were significantly more effective than non-biological treatments in improving physical function in RA. The study conducted a meta-analysis of 35 studies, which included 8733 treated patients with RA and 4664 controls. More than 50% of patients treated with biologics experienced clinically significant improvement. Etanercept and rituximab were the most effective drugs both for patients who had never previously taken antirheumatic drugs and for those who showed an inadequate response to them.

[19]. Minocycline may act as a DMARD due to its action as a matrix metalloproteinase inhibitor (MMPI). Leflunomide is a recent addition to the nonbiologic DMARDs and has activity similar to that of SSZ and MTX. Most of these drugs have been shown to improve signs and symptoms (as well as quality of life) and significantly slow the radiographic progression of RA.

Biological DMARDs: TNF inhibitors. TNF inhibitors, which bind TNF and thus prevent it from interacting with its receptors, include the following: etanercept, infliximab, adalimumab, certolizumab, golimumab. The results of one study noted that the use of anti-TNF therapy may double the risk of septic arthritis in patients with RA, with this risk being highest in the first months of therapy.

Adalimumab. A 5-year analysis of an open-label extension (OLE) study concluded that a 52-week delay in adding adalimumab to concomitant methotrexate therapy contributed to worse radiographic, functional, and clinical outcomes in patients with active RA. [12] According to a study of 221 consecutive patients with RA, blood levels of adalimumab between 5 and 8 mcg/mL have the greatest effect on disease activity.

In the study, adalimumab trough levels greater than 8 mcg/mL had no additional beneficial effect on disease activity. [13, 14] Certolizumab.Fleischmann et al. We found that certolizumabmonotherapy was effective in reducing the signs and symptoms of active RA in patients who had failed DMARD therapy. [15] In this study, 200 patients were randomized 1:1 to receive certolizumab 400 mg or placebo every 4 weeks for 24 weeks.

At 24 weeks, 45.5% of the certolizumab group achieved 20% improvement according to ACR criteria, compared with 9.3% of the placebo group. Statistically significant differences were observed already from weeks 1 to 24 [15].

Biological DMARDs: non-TNF agents: Rituximab. Rituximab is most often used in combination with methotrexate. It has been shown to be effective in reducing signs and symptoms in adult patients with moderately to severely active RA who have had an inadequate response to therapy with one or more TNF inhibitors. [21,] The ORBIT trial of 295 biologic-naive patients with RA found that initial treatment with rituximab was noninferior to initial TNF inhibitor treatment and was cost-saving over 12 months.

Treatment with rituximab may deplete CD20+ B cells. A study by Bingham et al. Showed that polysaccharide and primary immunization should be given before rituximab infusions to maximize treatment efficacy. [25] A study found that the response to pneumococcal polysaccharide vaccine was less in RA patients treated with rituximab and methotrexate (57% showed a two-fold increase in titer in response to 1 or more serotypes) than in patients treated with methotrexate alone (82%). **Anakinra**.Anakinra is a recombinant non-glycosylated form of the human IL-1 receptor antagonist (IL-1ra). IL-1ra occupies the IL-1 receptor without firing it and prevents IL-1 from binding to the receptor. In clinical trials, significant responses were observed in approximately 40% of patients with RA. AbataceptAbatacept is a selective costimulation modulator that inhibits T cell activation by binding to CD80 and CD86, thereby blocking their interaction with CD28. Interaction with CD28 provides the signal necessary for full T cell activation, which is involved in the pathogenesis of RA.

Maintenance doses of abatacept can be administered as a monthly intravenous (IV) infusion or by the patient as a weekly subcutaneous injection. [26]. Tocilizumab. Tocilizumab, an IL-6 receptor inhibitor, is available as an intravenous infusion or subcutaneous injection. It is indicated for moderate to severe active RA in adults who have had an inadequate response to treatment with one or more TNF antagonists. It can be used alone or in combination with MTX or other DMARDs.

However, Dougados et al. We found that in patients with active RA, combination therapy with intravenous tocilizumab and methotrexate did not produce better clinical results than tocilizumabmonotherapy and was more often associated with increased transaminase levels. [16 [29] [14,22. Corticosteroids: Corticosteroids are potent anti-inflammatory drugs that are commonly used in patients with RA to reduce the time before DMARD treatment becomes effective. These agents are effective adjuncts to DMARD or NSAID therapy.

NSAIDs interfere with prostaglandin synthesis by inhibiting the enzyme cyclooxygenase (COX), reducing swelling and pain. However, they do not slow down joint destruction and are therefore not sufficient to treat RA when used alone. Like corticosteroids, the dose of NSAIDs can be reduced or discontinued if DMARD therapy is successful. There are dozens of NSAIDs available, which can be divided into several different groups of compounds. CommonlyusedN SAIDsincludeibuprofen, naproxen, ketoprofen, piroxicamanddiclofenac

Adverse Effects: Coxibs, with their COX-2 selectivity, have been shown to be clinically effective and associated with reduced gastrointestinal (GI) toxicity, the main adverse event associated with the use of non-selective COX inhibitors (i.e., NSAIDs). Other side effects, such as water retention, hypertension, and abnormal transaminase levels, are observed with both non-selective COX inhibitors and selective COX-2 inhibitors. Analgesics: Acetaminophen, tramadol, codeine, opiates, and other pain relievers can also be used to reduce pain. Theseagentsdonotaffectjointswellingordestructio.

Conclusions

Experimental Treatments: Despite significant advances in recent decades, RA continues to be a chronic disease. It remains active in many patients whose conditions are partially or completely unresponsive to DMARDs. Therefore, the active search for new therapeutic agents continues. Several novel biological agents targeting CD20 B cells are under investigation, including atascept, AMG 623, B3- FCc, Br3-Fc, belimumab, epratuzumab, ofatumumab, ocrelizumab, and TRU-015. Further studies are needed to determine the safety and effectiveness of drugs in patients with RA20,21]. Rheumatoid arthritis, classification, etiology, risk factors, pathogenesis, clinical picture, diagnosis, treatment.

Bibliography

1. Burmester G. R. et al: Identification of three major synovial lining cell populations bymonoclonal antibodies directed to la antigens and antigens associated with monocytes/macrophages and fibroblasts. Scand J Immunol. 1983;17:69.
2. Harris Jr. E. D:. Rheumatoid arthritis: The clinical spectrum, in Textbook of Rheumatology, W. N. Kelley et al (eds). Philadelphia, Saunders. 1981:928-963.

3. Kurasaka M., Ziff M.: Immunoelectron microscopic study of the distribution of T-cellsubsets in rheumatoid synovium. J Exp Med. 1983:158:1191.
4. Legrand L. et al: HLA-DR genotype risks in. seropositive rheumatoid arthritis. Am J Hum Genet. 1984:636:690.
5. Lindblad S. et al: Phenotypic characterization of synovial tissue cells in situ in differenttypes of synovitis. Arthritis Rheum. 1983:26:1321.
6. Poulter L. W. et al: The involvement of interdigitating (antigen-presenting) cells in thepathogenesis of rheumatoid arthritis. Clin Exp Immunol. 1983:51:247.
7. Rothschild B.,MasiA. T.: Pathogenesis of rheumatoid arthritis: A vascular hypothesis. Semin Arthritis Rheum. 1982;12:11.
8. Utsinger P. D. et al (eds): Rheumatoid Arthritis. Philadelphia, Lippincott. 1985
9. Howard R Smith, MD Director of the Lupus Clinic, Department of Rheumatic and Immunologic Diseases, Cleveland Clini.
10. Adam Brown, MD Fellow, Department of Rheumatology,: American College of Rheumatology, American Medical Association
11. Herbert S Diamond, MD Visiting Professor of Medicine, Division of Rheumatology, State University of New York Downstate Medical Center;: Alpha Omega Alpha, American College of Physicians.
12. Robert J Nowinski, DO Clinical Assistant Professor of Orthopaedic Surgery,: American Academy of Orthopaedic Surgeons, American College of Osteopathic Surgeons.
13. Disclosure: Tornier Grant research funds Other; Tornier Honoraria Speaking and teaching.
14. Robert E O'Connor, MD, MPH Professor and Chair, Department of Emergency Medicine, University of
15. Sigma Theta Tau International.
16. Roberto Sandoval, MD Consulting Staff, Department of Emergency Medicine, American College of Emergency Physicians and American Medical Association.
17. Joseph E Sheppard, MD Professor of Clinical Orthopedic Surgery,: American Academy of Orthopaedic Surgeons, American Society for Surgery of the Hand, and Orthopaedics Overseas.
18. Francisco Talavera, PharmD, PhD Adjunct Assistant Professor, University of Nebraska Medical Center College of Pharmacy; Editor-in-Chief, Medscape Drug Reference.
19. Roman V Voytsekhovskiy, MD Fellow in Hand Surgery, Department of Orthopedic Surgery, Rush University Medical Center.
20. Eleby R Washington III, MD, FACS Associate Professor, Department of Surgery,: American Academy of Orthopaedic Surgeons, American College of Surgeons, American Medical Association, International College of Surgeons, and National Medical Association.
21. Richard Worthington MD, Department of Emergency Medicine, Wood County Hospital.Richard Worthington is a member of the following medical societies: American College of Emergency Physicians, Ohio State Medical Association, and Society for Academic Emergency Medicine.
22. Ahmedova, D. I., and Sh A. Rahimjanov. "Growth and development of children. Methodical recommendation." (2006).
23. Ахмедова, Д. И. "Физическое развитие и состояния здоровья детей, занимающихся спортом." Сб. тезисов VI съезда педиатров Республики Узбекистан (2009): 109-110.