Journal of Biomedical Sciences | ISSN: 2960-9356
Research Article Peer-review, Open Access

Modern Aspects of the Pathogenesis of Juvenile Rheumatoid Arthritis

Sayidova Madina Xamrokulovna [1]

Abstract

One of the most common rheumatic diseases, the growth trend of which is currently observed in children, is juvenile arthritis – arthritis of unknown cause, lasting more than 6 weeks, developing in children under the age of 16 years, excluding other joint pathology. In recent years, the role of connective tissue dysplasia as a background pathology in the development of various diseases has been actively discussed.

Key words: juvenile rheumatoid arthritis, children, joints, pathogenesis.

[1] Bukhara State Medical Institute

Juvenile idiopathic arthritis (JIA) is a chronic childhood arthritis. Its pathogenesis is very complex, it involves not only immune cells, but also various types of parenchymal cells, and it is influenced by both genetic and environmental predispositions. The clinical spectrum from inflammation to related conditions is largely mediated by cytokines, including interleukin (IL)-6. Fluctuations in IL-6 and related molecules can modulate pathogenesis and clinical presentation both positively and negatively. The recent clinical impact of IL-6 blockade on JIA marked the beginning of a change in the therapeutic paradigm.

The purpose of the study: to study the pathogenetic mechanisms of the formation of JRA in children.

Research materials and methods: A review of foreign materials and literature sources on medical research from the MEDLINE and PubMed databases over the past 15 years (2010-2025) has been conducted.

Results.

Juvenile idiopathic arthritis (JIA) is a disease that occurs in childhood and is characterized by chronic inflammation of joints and many organs [1]. Like other inflammatory diseases, the immunological pathogenesis of JIA is caused by a multiphase dysregulation of the immune system affecting both innate and adaptive branches. Cytokines play a central role in this multi-stage, multiphase cascade reaction, forming this complex disease state.

Interleukin (IL)-6 is a pleiotropic cytokine that mediates acute phase reactions. It is produced not only by immune cells as a mediator of cell proliferation, differentiation, activation, and survival, but also by various types of parenchymal cells such as endothelial cells, keratinocytes, adipocytes, and mesangial cells as an innate response through pattern recognition receptors. It also modulates the production of acute phase proteins, stimulates collagen production from fibroblasts, and causes vascular endothelial activation and osteoclast differentiation [2].

In general, vaccination with live-attenuated vaccines is prohibited in patients treated with biologic DMARDs, including tocilizumab, because of the risk of infection. A retrospective, multi-center survey detected three tocilizumab-treated soJIA patients with inactive disease who received live-attenuated vaccines. One patient who received an oral polio vaccine had diarrhea 10 days after the vaccination. Another soJIA patient who was injected with varicella vaccine experienced a mild disease flare. The last patient received an MMR booster without any adverse event. Inactivated vaccines are safely injected into patients with soJIA receiving biologic DMARDs. Inoculation of flu vaccine during tocilizumab therapy can have the same immune response as healthy subjects without adverse events [3].

IL-6 acts on cells through the gp130 cell membrane by binding to the membrane-bound IL-6 receptor, which is limited in leukocytes and hepatocytes. On the other hand, IL-6 can act in a similar way through the soluble type of IL-6 receptor and gp130. Since gp130 is expressed everywhere, IL-6 has the ability to act on all cells. Stimulation of IL-6 by an adapter protein binding to gp130 leads to activation of the JAK/STAT pathway and the JAK-SH2 pathway, a domain-containing protein tyrosine phosphatase-2-mitogen-activated protein kinase, which leads to cytokine production. This signaling is positively regulated by ADAM 17, causing cleavage of the IL-6 membrane protein receptor (IL-6R) [4] and the splicing variant of soluble (s)IL-6R in circulating microvesicles [5] and negatively regulated by soluble gp130 [6] and SOCS3.

The International League of Rheumatology Associations (ILAR) identifies subtypes of autoimmune inflammatory diseases determined by the number of affected joints, the presence of systemic symptoms, and the detection of rheumatoid factor (RF). JURA is divided into subforms: oligoarticular (persistent or widespread), polyarticular (RF-negative or RF-positive), systemic (sJIA), psoriatic arthritis and arthritis associated with enteritis, each of which differs in the genetic susceptibility and severity of arthritis. Any arthritis that does not fit into these categories or corresponds to > 1 subtype is considered undifferentiated [7].

In 2019, the Consensus of the International Organization for Research in Pediatric Rheumatology (PRINTO) revised the ILAR classification criteria and proposed to identify this set of signs as early ANA-positive Jurassic. Other jurassic disorders identified according to these preliminary criteria include sURA, RF-positive JURASSIC associated with enthesitis/spondylitis. Arthritis lasting more than 6 weeks that does not meet the criteria is grouped as "Other JRA", and the one that meets more than one criterion is "unclassified JRA". The PRINTO consensus identifies JRA not as a separate disease, but as a group of different disorders, the diagnosis of which does not require counting joints or the presence of arthritis. The onset of the disease was changed to the age of 18 years [8].

There is little information on the tapering and withdrawal of tocilizumab for JIA treatment. A retrospective study of tocilizumab for soJIA reported that four-week intervals of tocilizumab therapy could be available in cases with milder clinical courses that present in the inactive stage with >30% improvement in the ACR Pedi score just 2 weeks after the first tocilizumab infusion. Using this tapering method, seven of 25 cases finally terminated tocilizumab therapy without increasing glucocorticoids, suggesting that in certain types of soJIA, tocilizumab can be administered with longer intervals and eventually be discontinued. An extensive analysis revealed that, with four-week tocilizumab therapy intervals, successful cases have distinct baseline characteristics in laboratory variables, such as white blood cell count and levels of hemoglobin, total protein, albumin, CRP, ESR, ferritin, and LDH, compared with unsuccessful cases. This analysis also revealed differences in the MAS prevalence and in

clinical findings, such as hepatomegaly and splenomegaly, as well as in the reduction rate of peripheral granulocyte count at 2 weeks post-tocilizumab induction. Furthermore, several baseline status and follow-up data were identified as factors predicting achievement of tocilizumab-off remission, referring to the condition without fever, lymphadenopathy, CNS involvement, or abnormal coagulation test results at baseline in addition to a lack of history of MAS and persistent low disease activity in clinical course [1].

Serological biomarkers in the tissues of patients with JRA can be divided into those that are stable and persistent throughout the course of the disease (including antibodies such as RF), and those that change over time and disease activity (including cytokines such as IL18). ANA, RF, anticyclic citrullinated peptide (anti-CCP) and antibodies against mutated citrullinated vimentin (anti-MCV) have been reported to have a non-systemic pathogenesis of JRA. RF is an antibody specific to the Fc fragment of IgG; It was first described as a key serological marker in adult rheumatoid arthritis (RA) patients, and then identified in a small subgroup of patients with pURA (only 5% of the total number of patients with JRA. RF-positivity is associated with a severe prognosis of JIA and rapid formation of bone erosions [9].

IL-6 affects bone metabolism, causing increased bone resorption and inhibition of ossification. This can also be explained by the direct effect of IL-6 on the growth aspect of JIA, as growth improvement was noted in >70% of JIA patients treated with tocilizumab for 2 years. In addition, patients treated with tocilizumab showed catching-up growth along with improved levels of IGF-1, osteocalcin, type I collagen C-telopeptide, COMP (as a marker of cartilage) and BAP (as a marker of bone metabolism), indicating that IL-6 plays a pathogenic role in growth. in addition to its role in inflammation in JIA. [10].

Conclusion

IL-6 is involved in both local and systemic inflammation of the JIA pathogenesis, as well as in JIA complications such as RA and PsA. Although the detailed mechanism is still unknown, the choice of an IL-6 inhibitor should be based on the type, time, phase of the disease and the case, taking into account biological and genetic information. Future studies will identify an adequate therapeutic strategy by answering the questions of whether IL-6 signaling blockades affect these roles, how they function in JIA, and how JIA pathogenesis can be altered by IL-6.

References

1. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur AM, Suarez-Almazor ME, Woo P, Международная лига ассоциаций ревматологии Международная лига ассоциаций ревматологии классификация ювенильного идиопатического артрита: второй пересмотр, Эдмонтон, 2001. J Rheumatol. 2004;31(2):390–392. [PubMed] [Google Scholar]
2. Праккен Б., Альбани С., Мартини А. Ювенильный идиопатический артрит. Ланцет. 2011;377(9783):2138–2149. дои: 10.1016/S0140-6736(11)60244-4. [DOI] [PubMed] [Академия Google]
3. Stoll ML, Punaro M. Псориатический ювенильный идиопатический артрит: история двух подгрупп. Curr Opin Rheumatol. 2011;23(5):437–443. doi: 10.1097/BOR.0b013e328348b278. [DOI] [PubMed] [Google Scholar]
4. Мартини А. Системный ювенильный идиопатический артрит. Autoimmun Rev. 2012;12(1):56–59. doi: 10.1016/j.autrev.2012.07.022. [DOI] [PubMed] [Google Scholar]
5. Равелли А., Миноя Ф., Дави С., Хорн А., Бовис Ф., Писторио А. и др. 2016 Критерии классификации синдрома активации макрофагов, осложняющего системный ювенильный идиопатический артрит: Европейская лига против ревматизма/Американский колледж ревматологии/Совместная инициатива международных организаций по испытаниям детской ревматологии. Артрит и ревматология (Хобокен, Нью-Джерси). 2016;68(3):566-76. [DOI] [

PubMed]

6. Eng SW, Duong TT, Rosenberg AM, Morris Q, Yeung RS. Биологическая основа клинической гетерогенности при ювенильном идиопатическом артрите. Артрит и ревматология (Хобокен, Нью-Джерси). 2014;66(12):3463–75. [DOI] [Бесплатная статья PMC] [PubMed]
7. Martini A, Ravelli A, Avcin T, Beresford MW, Burgos-Vargas R, Cuttica R, Ilowite NT, Khubchandani R, Laxer RM, Lovell DJ, Petty RE, Wallace CA, Wulffraat NM, Pistorio A, Ruperto N, для Международной организации по испытаниям в области детской ревматологии (PRINTO) На пути к новым критериям классификации ювенильного идиопатического артрита: первые шаги, международный консенсус Международной организации по испытаниям в области детской ревматологии. J Rheumatol. 2019;46(2):190–197. doi: 10.3899/jrheum.180168. [DOI] [PubMed] [Google Scholar]
8. Twilt M, Pradsgaard D, Spannow AH, Horlyck A, Heuck C, Herlin T. Толщина суставного хряща и автоматизированное определение костного возраста и здоровья костей при ювенильном идиопатическом артрите. Электронный журнал детской ревматологии. 2017;15(1):63. doi: 9.1186/s12969-017-0194-9. [DOI] [Бесплатная статья PMC] [PubMed] [Google Scholar]
9. Swidrowska-Jaros J, Smolewska E. Новый взгляд на ангиогенез при ювенильном идиопатическом артрите. Центрально-европейский журнал иммунологии. 2018;43(3):325–330. doi: 10.5114/ceji.2018.80052. [DOI] [Бесплатная статья PMC] [PubMed] [Google Scholar]