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Pathogenetic mechanisms of biological agents in managing of relapsing polychondritis

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ABSTRACT

Relapsing polychondritis (RPC) is an autoimmune disease characterized by the inflammation of cartilaginous tissues and other tissues rich in proteoglycan. Concomitant diseases, particularly myelodysplasia or systemic autoimmune disease, can be detected in one-third of the patients with RPC. Unlike adults, RPC in children is less often associated with other autoimmune diseases. The diagnosis of RPC is established using the McAdam criteria (1976) or Damiani criteria (1979). The basis of the pathogenesis of RPC is an autoimmune reaction, which is initially directed against cartilage and then spreads to non-cartilaginous tissues. One of the elements in the pathogenesis of RPC is the mechanical trauma of cartilage, resulting in the release of pro-inflammatory cytokines (tumor necrosis factor alpha, interferon-γ, interleukin-8, and macrophage inflammatory protein 1) and local inflammation followed by the formation of auto-antibodies in a patient with a genetic predisposition. In the treatment of RPC, steroids, non-steroidal anti-inflammatory drugs, and colchicine are used and, if these are ineffective, immunosuppressants are prescribed. The most effective anti-cytokine drugs used in the treatment of RPC are tumor necrosis factor-alpha (TNF-α) inhibitors, IL-1 receptor antagonists, an inhibitor of the co-stimulatory pathway of T-lymphocyte activation, and monoclonal antibodies against the IL-6 receptor. Given the fact that management of these patients is very complex, the aim of the study is to review available data on pathogenetic mechanisms of biological agents in the management of relapsing polychondritis.

Key words: Relapsing polychondritis, clinics, etiopathogenesis, biological agents.

Recurrent polychondritis (RP) is a rare autoimmune disease, mainly affecting hyaline, elastic and fibrous cartilaginous tissues [1-5]. There may also be inflammation of other organs, whose tissues contain a lot of proteoglycan, such as the eyes, heart, blood vessels, inner ear and kidneys. One third of patients with RP have a concomitant disease, including systemic vasculitis, dermatological or hematological diseases, and other systemic rheumatic diseases (Fig.). These diseases can precede or be simultaneously present with

Recurrent polychondritis does not have pathognomonic clinical, radiologic, or histopathological signs, and so the diagnosis is made on the basis of a complex of clinical manifestations, laboratory data, radiological data and a biopsy of cartilaginous tissue. Known diagnostic criteria are the original "so-called" McAdam criteria. To diagnose RP, 3 or more clinical signs are necessary. Damiani et al. (1979)

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supplemented these criteria by including histological confirmation and response to therapy (Table).

The Damiani criteria are also used to diagnose RP in children. Despite the fact that RP in children is rare, more than 44 cases have been described in the English-language literature. In childhood, the damage caused to the respiratory tract (trachea, larynx) presents the greatest severity. Endotracheal intubation, bronchoscopy and biopsy can serve as a trigger for the disease. Also in the literature it is noted that the onset of the disease in childhood is more common in girls than in boys. Unlike adults, RP in children is less often associated with other autoimmune diseases [6–8].

Figure. Systemic diseases associated with relapsing polychondritis

Таблица
Table

Criteria for diagnosing relapsing polychondritis

Author	Criteria
L.P. McAdam et al.	Relapsing chondritis of both auricles Non erodible inflammatory polyarthritis Chondritis of nasal cartilages Eye inflammation: conjunctivitis, keratitis, scleritis, uveitis Chondritis of respiratory passages: laryngeal, tracheal cartilage Cochlear or vestibular damages: sensory neural hearing loss, ringing in the ears, dizziness
L.P. McAdam et al. [9]	Three out of six criteria are necessary for a diagnostic assessment
J. M. Damiani et al. [10]	Three out of six McAdam et al. [9] criteria or one out of six McAdam et al. [9] criteria and positive histological confirmation or two out of six McAdam et al. [9] criteria and the response to corticosteroid or dapsone

PATHOPHYSIOLOGY

Pathophysiology of RP still remains controversial and poorly understood. In the case of RP, inflammatory infiltrate in the affected tissue is polymorphic and consists of lymphocytes (mainly CD4 + T cells), macrophages, neutrophils and plasma cells. Infiltration of tissues with various cellular and humoral factors leads to the release of enzymes, such as metalloproteinase of intercellular substance and reactive oxygen intermediate (by inflammatory cells and chondrocytes), which ultimately leads to the destruction of cartilage and other proteoglycan-rich tissues [11]. The main hypothesis about the pathophysiology of RP is an autoimmune reaction, which is initially directed against the cartilage and then spreads to non-cartilaginous tissues [11].

ETIOPATHOGENESIS

Etiopathogenesis of RP is a combination of several factors, including genetic predisposition, trigger factor and autoimmunity. Trigger fac-

tors can be chemical, toxic and infectious agents or physical (direct injury). Recently, cases of RP have been reported [12] after trauma to the auricle and [13] intravenous administration of biologically active substances (eg chondroitin and glucosamine), which can have a direct toxic effect on the cartilage. This suggests that there is a direct link between trauma and the onset of autoimmune processes. Canas et al. [14] examined patients with RP and found that patients with a history of cartilage trauma had more signs of autoimmune diseases than those who did not have an injury. Consequently, the possible mechanisms of RP include the release of cryptogenic antigen, the recognition of pathogenic structure and metabolic changes caused by trauma [15]. The disease onset in children was described after bronchoscopy and endotracheal intubation, which can be a trigger [6].

The involvement of cartilaginous structures rich in proteoglycan in the pathological process in case of RP is explained by activation of the humoral component of the immune system. Circulating and tissue antibodies to type II, IX and XI collagen were detected in patients with RP using the method of indirect immunofluorescence [16 - 18]. Studies have shown that an increased level of cartilage-specific matrix protein-1 in the serum can be detected in patients with RP, especially in the active phase [19 - 20]. However, neither anti-collagen antibodies (mainly Type II, including other types - IX, X and XI), nor antibodies to matriline-1 are sensitive enough for use in diagnostic purposes, since they are found in a limited number of patients, and they are not specific for RP. For example, serum antibodies to type II collagen that are found in approximately 30% of patients with RP can also be diagnosed in rheumatoid arthritis [21, 22]. The levels of serum chemoattractant protein 1 (MCP-1), macrophage inflammatory protein beta-1 (MIP-1beta) and interleukin-8 (IL-8) are increasing during the active phase of the disease, emphasizing the role of monocytes and macrophages and their involvement in injured tissues [23].

In addition to antibodies and humoral immunity, which are of a particular importance in the pathogenesis of the disease, cellular immunity can maintain inflammation in the cartilage [24 - 26]. T cell activation has been shown to result in T helper 1 (Th1) cytokines containing tumor necrosis factor alpha, interferon-γ, interleukin-8, and macrophage inflammatory protein 1 in RP [27, 28]. We can assume that damage to the cartilage comprising chondrocyte epitopes leads to the release of cytokines and local inflammation followed by the formation of autoantibodies in a patient with a genetic predisposition [28].

DRUG THERAPY FOR PATIENTS WITH RP

Due to the lack of a clinical protocol, treatment of RP remains mainly experimental, and its main goal is to reduce the frequency and intensity of disease exacerbation, as well as to prevent the development of irreversible consequences. It is difficult to assess the effectiveness of treatment, due to the unpredictable nature and spontaneous course of the disease.

Depending on the clinical picture, the pharmacological treatment of RP can include steroids, nonsteroidal anti-inflammatory drugs, colchicine and, if they are ineffective, immunosuppressant drugs such as methotrexate, cyclophosphamide, azathioprine, dapsone, cyclosporine, mycophenolate mofetil are prescribed[1, 3]. In pediatric practice, in most of described cases, patients were prescribed a combination of non-steroidal anti-inflammatory drugs, steroids and methotrexate [7]. Although there are many drugs used to treat RP, in this article we will consider only anticytokine therapy.

Inhibitors of tumor necrosis factor-alpha (TNFα). It is reported that this group of biological drugs was the most effective for RP treatment. About 50 clinical cases have been announced, mainly treated with infliximab and, to a lesser extent, etanercept and adalimumab. Infliximab is a chimeric monoclonal antibody (AT). Taking infliximab (3 - 10 mg/kg) every 6 - 8 weeks resulted in partial or total recovery in more than 50% of cases of arthritis, auricular chondritis, chondritis of the nasal septum, laryngotracheal chondritis, episcleritis, scleritis, including necrotizing scleritis, ulcerative keratitis, cutaneous vasculitis, meningitis, encephalitis and aortitis with a decrease in the level of C-reactive protein [26 - 36]. The onset of action was noted within a month with good outcomes, except for one death, as a result of sepsis [29]. The efficacy of infliximab is maintained for about 9 months or 3 years [29]. Etanercept (a drug containing two proteins: the human tumor necrosis factor receptor and the Fc site of human immunoglobulin G1) demonstrated similar efficacy and tolerability when taking 50

mg/week as well as Adalimumab, recombinant monoclonal antibody, whose peptide sequence is identical to human lgG1 [29 - 30, 34 - 38]. It must be stressed that there were some complications (infusion complications, angioedema) among children after taking infliximab, and as a result, it was replaced with etanercept and a good therapeutic effect was obtained in most patients [8].

The interleukin-1 receptor antagonist: Anakinra. The IL-1 receptor antagonist (IL-1RA) is a protein that binds to the cell surface of the IL-1 receptor (IL-1R) and prevents activation of the cell. About 10 clinical cases of RP treated with anakinra (100 mg/day) have been announced [29 - 30, 37, 39 - 43]. This drug was used because anti-TNF-α therapy showed a lack of efficacy.

Anakinra was partially or completely effective in more than 50% cases of necrotizing cutaneous vasculitis, arthritis, auricular chondritis, nasal septum chondritis, laryngotracheal chondritis and several ophthalmic diseases [29 - 30, 37, 39 - 41, 43]. However, in a study published by Moulis et al., anakinra was ineffective in two patients [30].

Inhibitors of co-stimulating signaling pathway for T-lymphocyte activation: Abatacept. Abatacept is a soluble protein consisting of the extracellular domain of the 4-cytotoxic T-lymphocyte antigen (CTLA-4) bound to the modified Fc fragment of the IgG1 human. It binds to CD80 and CD86 molecules and prevents the activation of T cells. Three clinical cases of RP with partial or total efficacy of Abatacept have been announced according to Moulis et al. [30, 44]. More recently, Peng et al. reported using Abatacept in an open-label follow-up study involving four patients with RP [45]. Abatacept was administered at a dose of 125 mg subcutaneously weekly for 24 weeks, but two patients discontinued treatment before the end of the course: one patient discontinued therapy due to worsening of pulmonary and neurologic disease, and the second patient experienced exacerbation of pulmonary disease and orbital pseudo-tumour [45]. However, three out of four patients demonstrated an improvement in the clinical picture of chondritis according to the assessment. Abatacept was well tolerated, but the most common adverse event was the reaction at the injection site. Despite the limitations of these data, scientists suggest that Abatacept can be effective, at least for chondritis and inflammatory arthritis in RP. Further studies of this drug in RP are necessary with the exclusion of patients with pulmonary lesions [45].

Anti-interleukin-6 receptor monoclonal AT: Tocilizumab. Tocilizumab (8 mg/kg/month) is a humanized monoclonal anti-IL-6 receptor antagonist (IL-6R). It neutralizes the activity of IL-6. There have been reported about 10 clinical cases of RP treated with Tocilizumab [30, 46 - 51]. This drug was effective in treatment of refractory RP-associated arthritis, nasal chondritis, auricular chondritis, laryngotracheal chondritis, inflammatory eye diseases and aortitis [30, 46 - 51]. Wallace et al. put forward a hypothesis that the key to the possible therapeutic efficacy of Tocilizumab is the detection of an extremely high concentration of IL-6 in the blood serum and as an inhibitor it will be more effective than other biological agents [48]. Further studies of IL-6R blockade in RP will help identify subgroups of diseases that can respond to Tocilizumab treatment.

B-cell therapy: Rituximab. Rituximab is a chimeric monoclonal anti-CD20 protein that promotes B cell lysis. After the publication of two clinical cases, scientists suggested that rituximab may be effective in chondritis and aortitis associated with RP in patients refractory to anti-TNF-α therapy [52, 53]. However, rituximab was not effective in a retrospective study consisting of 9 patients. He underwent long-term treatment with high doses of steroids, and patients did not respond to at least two immunosuppressant drugs. The clinical picture of patients slightly improved after taking Rituximab [54]. The case of Rituximab in a child with RP is described in the literature. As a result, a positive effect was obtained after treatment, which proves the need for further research [55].

CONCLUSION

It is important to say that the use of anticytokine drugs in RP is still limited and has different effects. Clinical profiles of patients with RP included in these publications are different. For example, in a series of clinical cases published by Leroux et al, patients receiving rituximab were immune to high doses of steroids and did not respond to at least two immunosuppressants, while in Moulis et al. study, biological drugs were often administered as an immuno-

suppressant drug of the first line [30, 54]. Endpoints of treatment also differ from one publication to another. Consequently, it is impossible to draw a definite conclusion about the efficacy of the use of biological drugs in the Republic of Poland.

Diagnostic assessment of RP in children is difficult due to the peculiarities of the evolution of the clinical picture, and the presence of different phenotypes and endotypes of the disease, which differ from the adult population. Modern genetically-engineered biological drugs effectively suppress autoimmune inflammation, but cannot completely replace cytostatic therapy in patients with RP. A better understanding of the etiopathogenesis of this disease and the creation of international interdisciplinary cooperation will facilitate the conduction of more controlled studies necessary to prepare guidelines for the treatment of recurrent polychondritis.

CONFLICT OF INTEREST

The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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Патогенетические основы таргетной терапии рецидивирующего полихондрита

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РЕЗЮМЕ

Рецидивирующий полихондрит (РП) – редкое аутоиммунное заболевание, характеризующееся рецидивирующим воспалением хрящевой и других, богатых протеогликаном тканей организма. Сопутствующие заболевания, в частности миелодисплазия или системные аутоиммунные заболевания, могут быть обнаружены у одной трети пациентов с РП. В отличие от взрослых у детей РП реже ассоциирован с другими аутоиммунными заболеваниями. Диагноз РП устанавливается с использованием критериев McAdam (1976) или Damiani (1979).

Основой патогенеза РП является аутоиммунная реакция, которая первоначально направлена против хряща и далее распространяется на нехрящевые ткани. Одним из звеньев патогенеза РП является механическая травма хряща, приводящая к высвобождению провоспалительных цитокинов (фактор некроза опухоли-α, интерферон-γ, IL-8 и макрофагальный воспалительный белок 1) и локальному воспалению с последующим образованием аутоантител у пациента с генетической предрасположенностью. В лечении РП используют стероиды, нестероидные противовоспалительные препараты, колхицин и, если они неэффективны, то назначают иммунодепрессанты. Наиболее эффективными антицитокиновыми препаратами, используемыми в лечении РП, являются ингибиторы фактора некроза опухоли-α, антагонисты рецептора IL-1, ингибитор ко-стимулирующего пути активации Т-лимфоцитов, моноклональные антитела против рецептора IL-6. Учитывая сложность ведения таких пациентов, целью данного обзора было осветить последние данные о патогенетических основах антицитокиновой терапии РП.

Ключевые слова: рецидивирующий полихондрит, клиника, этиопатогенез, биологическая терапия.

КОНФЛИКТ ИНТЕРЕСОВ

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