Editorial paper

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Usefulness of interleukin-1 blockade in autoinflammatory diseases

Alenka Gagro

Department of Pulmonology, Allergology, Clinical Immunology and Rheumatology, Department of Paediatrics, Children's Hospital Zagreb, Croatia

Interleukin-1: fifty years of discovery

It has been 50 years since the initial descriptions of what are now known as interleukin (IL)-1α and IL-1β [1]. These two unique inflammatory mediators, which share a common IL-1 receptor (IL-1R1), later became recognized as members of the much larger IL-1 family of cytokines that so far include 11 pro-inflammatory and anti-inflammatory cytokines, and 11 receptors [2, 3].

The importance of IL-1α and IL-1β was further supported by the discovery of mutations in genes encoding inflammasome-related proteins. Interleukin-1 driven monogenic autoinflammatory disorders lead to persistent activation of the NLPR3 or pyrin inflammasomes and subsequent activation of caspase 1, resulting in IL-1 release and autoinflammation. Other monogenic disorders such as those caused by mutations in *TNFRSF1A*, *MVK*, *PSTPIP1* and *CDC42* are considered as IL-1-associated autoinflammatory disorders since they lead to IL-1 activation through pathways other than direct inflammasome activation. A plethora of polygenic diseases appear to be mediated by IL-1 and respond to IL-1-targeted therapies also. These diseases include Still's disease, macrophage activation syndrome (MAS), Schnitzler syndrome, gout, recurrent pericarditis, chronic recurrent multifocal osteomyelitis, hidradenitis suppurativa, pyoderma gangrenosum and acne, Kawasaki's disease, Behçet's disease and syndrome of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) [4, 5].

Comparison of interleukin-1α and interleukin-1β

Various triggers (so-called damage- and pathogen-associated molecular patterns) have been identified as triggers of IL-1 secretion. Our understanding of IL-1-driven inflammatory responses and a rationale for IL-1 therapy rely on our deeper understanding of two cytokines, IL-1α and IL-1β, and their antagonist, IL-1RA. Interleukin-1α and IL-1β are encoded as precursors by distinct genes located on chromosome 2. They share 25% of their sequence and are able to bind and activate the same receptor (IL-1R1, CD121a). Cleavage of pro-IL-1β into active 17 kDa IL-1β is essential for its function. This process is mediated by caspase-1 in the inflammasome-dependent pathway and caspase-8 in the inflammasome-independent pathway. The major cell subsets that produce IL-1β are monocytes, macrophages, neutrophils and mast cells.

In contrast to pro-IL-1β, pro-IL-1α is functional and activates cells via IL-1R with 50% potency of IL-1β and of cleaved IL-1α. Interleukin-1α is constitutively expressed in keratinocytes, epithelial lung and gut cells, platelets and megakaryocytes, while myeloid cells express IL-1α upon activation. The function of IL-1α depends on its location. In the nucleus, IL-1α binds to chromatin and regulates cytokine expression downstream of NF-κB and AP-1, whereas in the cytoplasm it binds to mitochondrial cardiolipin to regulate NLRP3 inflammasome function and binds to its receptor on neighbouring cells if expressed on the cell membrane.

Interleukin-1 receptor A acts as an antagonist cytokine since it binds to IL-1R1 but does not recruit IL-1 receptor accessory protein (IL-1RAcP) and therefore does not elicit downstream signalling [4, 6].

Clinical and laboratory presentation of interleukin-1 driven diseases

The most common clinical presentation of IL-1 mediated autoinflammation is recurrent or chronic inflammation. The patients often present with fever, fatigue or malaise, skin changes (urticarial-like rash, acne), aphthae, musculoskeletal complaints and inflammation of serous membranes, the central nervous system and conjunctiva. Laboratory evaluation of patients during or even between attacks reveals elevated acute phase

Address for correspondence:
Alenka Gagro, Department of Pulmonology, Allergology, Clinical Immunology and Rheumatology, Department of Paediatrics, Children's Hospital Zagreb, V. Klaića 16, 10000 Zagreb, Croatia, e-mail: alenka.gagro@gmail.com
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markers, neutrophilia, and anaemia of chronic disease. In patients with MAS, hyperferritinaemia, increase in lactate dehydrogenase, low or dropping fibrinogen, pancytopenia and increased triglycerides point to this life-threatening complication. Delayed diagnosis and ongoing chronic inflammation can cause in some patients tissue damage, such as amyloid A amyloidosis [4].

Treat-to-target approach in interleukin-1 driven autoinflammatory diseases

The ultimate goal of therapy in IL-1 driven autoinflammatory diseases is to gain control of symptoms, normalize systemic inflammation, and minimize or prevent the development of organ damage. A treat-to-target (T2T) approach which could enable individualization of therapy has not been published by leading international societies except for familial Mediterranean fever [7, 8]. We lack sufficient evidence obtained by controlled trials of the efficacy of anti-IL-1 agents in preventing amyloidosis or their safety in pregnancy [4, 9].

Interleukin-1 inhibitors

Several IL-1 inhibitors have been developed, but the European Medicinal Agency approved the IL-1 receptor antagonist analogue anakinra and the IL-1β selective monoclonal antibody canakinumab (Table I). The selection of the IL-1 inhibitor depends on the specific pharmacologic mechanisms, pharmacokinetics, disease indications and costs. Unfortunately, we still lack appropriate head-to-head trials of the different IL-1 inhibitors.

Table I. Comparison of European Medicinal Agency approved indications for subcutaneous treatment between anakinra and canakinumab

Parameter	Anakinra	Canakinumab
Age (minimum)	8 months	2 years
Weight (minimum)	10 kg	No limit
Indications		
Rheumatoid arthritis	Yes	No
Cryopyrin-associated periodic syndromes	Yes	Yes
Familial Mediterranean fever (FMF)	Yes	Yes
Hyperimmunoglobulin D syndrome/mevalonate kinase deficiency	No	Yes
Tumour necrosis factor receptor associated periodic syndrome	No	Yes
Systemic juvenile idiopathic arthritis	Yes	Yes
Adult-onset Still's disease	Yes	Yes
Gouty arthritis	No	Yes
COVID-19	Yes	No

In depth knowledge of the pathogenesis of autoinflammatory diseases could help us choose the most suitable IL-1 inhibitor. For example, in patients with central nervous system inflammation, a drug of choice is anakinra as it penetrates the blood–brain barrier more efficiently. In children younger than 2 years of age, anakinra is so far the only option of treatment. Canakinumab offers better control of arthritis as well as better compliance due to (bi) monthly administration. The overall rate of response to IL-1 inhibitors depends on the condition treated and ranges from 50–75% in TNF receptor-associated periodic syndrome (TRAPS) and mevalonate kinase deficiency (MKD) to 90% in systemic juvenile idiopathic arthritis (sJIA) [10].

Anakinra

Anakinra differs from endogenous IL-1RA by addition of methionine at the amino terminus. It competitively inhibits binding of both IL-1α and IL-1β to IL-1R. Maximal plasma concentration after subcutaneous administration is 3–7 h. Due to a short half-life, daily therapy is required. Off-label indications for which anakinra is routinely employed in rheumatology include idiopathic recurrent pericarditis resistant to colchicine, autoinflammatory diseases without established genetic diagnosis, gout, severe presentation of multisystemic inflammatory syndrome in children, MAS, chronic granulomatous disease, cytokine release syndrome secondary to complications from CAR T-cell therapy and hidradenitis suppurativa [4]. In critically ill patients, off-label use of intermittent or continuous intravenous anakinra up to 10 mg/kg/day was reported. This approach enables better control of cytokine storm and avoidance of multiple, often painful subcutaneous injections [11].

Canakinumab

Canakinumab is a human IgG1/κ monoclonal anti-IL-1β antibody that has no cross-reactivity with other members of the IL-1 family, including IL-1. This drug directly competes with IL-1RI for IL-1β binding and neutralizes IL-1β with high potency and selectivity. Canakinumab has an estimated half-life of 22 days and this enables monthly injections in most of the patients.

Anti-drug antibodies to both IL-1 inhibitors can be detected in approximately 3% of patients; however, there are rarely neutralizing ADAs [4, 12]. Clinical experience indicates that patients who fail to respond to one IL-1 inhibitor may still respond to another.

Beware of serious adverse reactions to interleukin-1 inhibitors

Hypersensitivity reactions to IL-1 inhibitors such as drug rash with eosinophilia and systemic symptoms (DRESS) and anaphylaxis are rare and associated with HLA–DRB1*15. In some children with severe sJIA exposed to IL-1 inhibitors, an unusual, life-threatening lung disease has been reported. A warning clinical sign of this complication is newly onset tachydyspnoea, cough and acute erythematous digital clubbing [13].

Room for improvement and new kids on the block

Expert international societies regularly evaluate and publish recommendations for treatment of patients with IL-1 mediated and associated conditions. These recommendations should also include the T2T strategy, the most appropriate drug at onset or relapse of the disease, short- and long-term complications, validated disease activity scores, criteria for tapering and/or discontinuation of the treatment, improvement of quality of life and transition into adult care. Targeting single proteins in the IL-1 pathway is not sufficient in all patients. The importance of other cytokines (i.e. IL-18 and IL-36) in pathogenesis requires a different approach such as combination anti-cytokine therapy or small molecule inhibitors (for a list of candidate drugs and ongoing clinical trials see reference 3). Better knowledge on genetics, genotype-phenotype correlations, epigenetics and specific biomarkers should open new avenues for treatment of IL-1 driven diseases and even gene therapy.

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