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Expanding clinical spectrum and broadening therapeutic horizons

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Abstract

In 2010, important research into the systemic autoinflammatory diseases has confirmed and extended the role of IL-1 inhibition in hereditary autoinflammatory disorders, demonstrated a novel treatment for a dangerous complication, and expanded the spectrum of systemic autoinflammatory diseases while further implicating autoinflammation in the pathophysiology of the metabolic syndrome.

The systemic autoinflammatory diseases are a growing family of disorders characterized by a genetic predisposition towards excessive innate immune activation¹. First identified in the hereditary periodic fever syndromes, autoinflammation is increasingly recognized in common diseases, including gout and type 2 diabetes (T2D)², providing new opportunities to understand further mechanisms regulating innate immunity and inflammation. As we review the progress of 2010 in the field of autoinflammation, we consider the long-term efficacy and safety of interleukin-1 (IL-1) blockade in two prototypic Mendelian autoinflammatory diseases^{3,4}. We then turn to a promising new treatment for systemic amyloidosis, a potentially fatal complication of autoinflammation⁵. Finally, we discuss the data supporting the addition of atherosclerosis to the expanding spectrum of autoinflammatory diseases⁶.

The cryopyrinopathies are three overlapping autoinflammatory diseases—familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disorder (NOMID), also known as chronic infantile neurologic cutaneous and articular [CINCA] syndrome. The cryopyrinopathies are caused by mutations in *NLRP3*, leading to excessive activation of the NLRP3 inflammasome, a multiprotein complex responsible for the cleavage of pro-IL-1 β into mature IL-1 β . Therapeutic agents that block IL-1 have proven highly effective at eliminating systemic inflammation in short therapeutic courses in all three disorders^{7,8}. One of these agents, anakinra, is a recombinant IL-1 receptor antagonist.

In 2010, two groups reported similar results of retrospective, observational studies of long-term anakinra use in patients with MWS or NOMID^{3,4}. Neven and colleagues described the outcomes of 10 patients with NOMID, including two severely affected infants, who were treated with anakinra daily for 26–42 months³. Lepore and colleagues described nine patients with NOMID and four with MWS treated with anakinra for 12–58 months, as well as five NOMID patients who declined treatment⁴. In both studies, long-term anakinra

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therapy persistently ameliorated rash, arthralgia/arthritis, fever and elevated levels of acute phase reactants. Across both studies, only one disease flare was reported during anakinra treatment, no treated patient had development or exacerbation of neurosensory hearing loss (NSHL) or optic nerve atrophy, and three of 14 individuals with pre-existing NSHL experienced minor improvement in their auditory acuity after initiating anakinra therapy.

Excluding the infants, persistent neurologic findings prompted dose escalation, up to 3 mg/kg daily, in nine anakinra-treated NOMID patients in these trials. Although each of these nine subjects experienced improvement or stabilization of their neuroinflammatory features, none of these findings completely normalized. In contrast, two infants with severe NOMID treated aggressively with escalating doses of anakinra³—as high as 10 mg/kg daily—experienced normalization of acute phase reactants and remission of clinical features, including neuroinflammation, throughout their follow-up period. Their dramatic response to markedly higher doses of anakinra, without untoward events, suggests that such dosages of anakinra could provide additional benefit to NOMID patients with persistent neuroinflammation. The presence of structural or fixed lesions or inadequate dosing might account for incomplete response to anakinra. Alternatively, some manifestations of NOMID could be independent of IL-1 β . For example, both studies found that treatment with anakinra had no influence on the progression of pre-existing bony dysplasia, although no instances of new bony lesions were observed after initiation of anakinra therapy.

The long-term safety of anakinra in the cryopyrinopathies was quite similar to that of its short-term use^{7,8}. No serious or opportunistic infections or malignancies were reported among individuals treated with anakinra. Collectively, the most common adverse event was localized injection site reactions.

Given the sustained efficacy and safety of anakinra therapy in MWS and NOMID, its indefinite continuation should be the standard of care in the treatment of these disorders. The lack of disease progression over nearly 3 years of treatment in the two aggressively-treated infants raises the possibility that early intervention may prevent the chronic features of NOMID, such as aseptic meningitis, amyloidosis and NSHL. The magnitude of improvement in prognosis and quality of life conferred by anakinra is underscored by progressive disability noted in the five patients who declined treatment⁴.

2010 also witnessed what promises to be a key therapeutic breakthrough in one of the most serious complications of autoinflammation: systemic amyloidosis. Recurrent inflammation can culminate in tissue deposition of fibrils derived from a misfolded acute phase protein, serum amyloid A. AA amyloid deposition is a dynamic process involving both deposition and resorption, and previous evidence has shown that aggressive anti-inflammatory treatment can sometimes induce regression of AA amyloid deposits⁹. The plasma glycoprotein serum amyloid P component (SAP) is a universal constituent of all types of amyloid plaques, and potentiates the amyloidogenic process.

A study by Bodin and colleagues⁵ tested a two-step therapeutic strategy for amyloidosis that targeted SAP by first pharmacologically depleting circulating levels of SAP with the bivalent crosslinker CPHPC¹⁰, and then subsequently administering anti-human-SAP antibodies. In mice transgenic for human SAP, an experimental model of systemic AA amyloidosis, this treatment regimen produced almost complete regression of hepatic and splenic amyloid deposits 4 weeks following anti-SAP treatment, whereas no such regression was observed in either the IgG isotype-treated or untreated control groups. Within 24 hours of treatment, an intense inflammatory infiltrate composed largely of macrophages was present in the amyloid deposits. At 48 hours, multinucleated giant cells were observed, with evidence of complement-mediated endocytosis of AA amyloid fibrils, and by day 7, the

majority of residual amyloid was located in the cytoplasm of the remaining giant cells. There was near-complete regression of amyloid deposits by day 16, at which time the authors also noted resolution of the monocytic infiltrates and restoration of apparently normal tissue architecture. A similar response to anti-SAP treatment was observed in non-transgenic, human-SAP-primed AA amyloidotic mice.

This study demonstrates the efficacy of an SAP-directed approach to treating amyloidosis in an experimental model of systemic AA amyloidosis. The investigators demonstrated that macrophages are essential to the amyloid plaque regression, and that the process of antibody recognition and clearance is primarily complement-mediated. No adverse outcomes of this treatment were apparent, as indicated by the equivalency of survival and body mass data between the treated and untreated groups of mice. These strikingly successful results strongly support the concept that amyloid deposition is reversible, and the initiation of clinical trials in humans will be of great interest.

Duewell and colleagues substantially advanced the field of autoinflammatory diseases by demonstrating an important role for the NLRP3 inflammasome in atherosclerosis⁶. In their seminal report, these authors showed that crystalline cholesterol induces NLRP3-activation and IL-1 β secretion, and that these events are essential to diet-induced atherosclerosis in mice. Using confocal fluorescence and reflection microscopy, this study established the presence of cholesterol crystals in the earliest lesions of the atherosclerosis-prone ApoE-deficient mice, building the case for their causal, rather than epiphenomenal role in pathogenesis. In this mouse model, atherogenesis was dependent on the presence of hematopoietic cells expressing various genes in the IL-1 pathway. The authors demonstrated that cholesterol crystals activated NLRP3 in primed human and mouse immune cells, resulting in secretion of IL-1 β .

Unlike crystalline cholesterol, Duewell *et al.* demonstrated that oxidized LDL (oxLDL) could dually prime and activate the NLRP3 inflammasome *in vitro*, resulting in secretion of mature IL-1 β . Although the mechanism of cellular priming by oxLDL was not experimentally addressed, the authors demonstrated that its activation of the NLRP3 inflammasome depended on lysosomal conversion of oxLDL into cholesterol crystals, which led to disruption of lysosomal membranes and NLRP3 inflammasome activation, as previously reported in silicosis and gout. The authors concluded that oxLDL alone is an adequate stimulus to drive atherosclerotic plaque formation.

The collective involvement of the NLRP3 inflammasome in the pathophysiologies of T2D, gout and now atherosclerosis nominates the caspase 1-cleaved cytokines and their pathways as therapeutic targets in these individual diseases. Moreover, the close relationship of T2D, gout and atherosclerosis with obesity and the metabolic syndrome raises the possibility of therapeutic IL-1 β blockade for this common malady of the Western World.

References

1. Kastner DL, Aksentjevich I, Goldbach-Mansky R. Autoinflammatory disease reloaded: a clinical perspective. *Cell*. 2010; 140:784–790. [PubMed: 20303869]
2. Masters SL, Simon A, Aksentjevich I, Kastner DL, et al. *Horror autoinflammaticus*: the molecular pathology of autoinflammatory disease. *Annu. Rev. Immunol.* 2009; 27:621–668. [PubMed: 19302049]
3. Neven B, et al. Long-term efficacy of the interleukin-1 receptor antagonist anakinra in ten patients with neonatal-onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, articular syndrome. *Arthritis Rheum.* 2010; 62:258–267. [PubMed: 20039428]
4. Lepore L, et al. Follow-up and quality of life of patients with cryopyrin-associated periodic syndromes treated with anakinra. *J. Pediatr.* 2010; 157:310–315. [PubMed: 20472245]

5. Bodin K, et al. Antibodies to human serum amyloid P component eliminate visceral amyloid deposits. *Nature*. 2010; 468:90–97.
6. Duewell P, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. *Nature*. 2010; 464:1357–1361. [PubMed: 20428172]
7. Goldbach-Mansky R. Blocking interleukin-1 in rheumatic diseases. *Ann N. Y. Acad. Sci.* 2009; 1182:111–123. [PubMed: 20074280]
8. Kubota T, Koike R. Cryopyrin-associated periodic syndromes: background and therapeutics. *Mod. Rheumatol.* 2010; 20:213–221. [PubMed: 20140476]
9. Lachmann HJ. Natural history and outcome in systemic AA amyloidosis. *New Engl. J. Med.* 2007; 356:2361–2371. [PubMed: 17554117]
10. Pepys MB, et al. Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis. *Nature*. 2002; 417:254–259. [PubMed: 12015594]

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Key advances

- In patients with cryopyrinopathies, sustained inhibition of interleukin-1 with anakinra is efficacious and safe, and early intervention could prevent the chronic features of these disorders^{3,4}
- A novel approach to treating amyloidosis that targets serum amyloid P component has shown great promise in an experimental model of systemic AA amyloidosis, a serious complication of autoinflammatory disorders⁵
- Evidence in support of a causal role for the NLRP3 inflammasome in the pathogenesis of atherosclerosis could add this disorder to the growing spectrum of systemic autoinflammatory diseases⁶