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Anti-inflammatory panacea? The Expanding Therapeutics of IL-1 Blockade

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Abstract

Purpose of review—Blockade of IL-1 signaling is one of the oldest biologic therapies, yet the use of these agents is on the rise as the role of IL-1 activation is being recognized in a wide spectrum of inflammatory disorders. This review will cover established and emerging uses of IL-1 antagonism in rheumatic diseases.

Recent findings—Expanding off-label indications for IL-1 blockade include neutrophil-dominant skin diseases including pyoderma gangrenosum, hidradenitis suppurativa, and pustular psoriasis. There is also increasing evidence for the use of IL-1 blockade in heart failure associated with rheumatic diseases. Somatic mosaicism in NLRP3 may explain the onset of later-in-life presentations of periodic fevers which are responsive to IL-1 blockade. Of importance, clinical response to anti-IL-1 therapy does not always denote protection from autoinflammatory disease complications such as macrophage activation syndrome or amyloidosis.

Summary—Indications for IL-1 blocking therapies will likely continue to broaden, but given the rarity of many rheumatic diseases which respond to such treatment, rigorous, large clinical trials for each indication are unlikely to occur. Thus, recommended use of these medications will often fall to the discretion of the astute physician. However, medication cost and hurdles of insurance approval, rather than drug efficacy, may be the primary limitation for more widespread use.

Keywords

IL-1 β ; IL-1 α ; auto-inflammatory; inflammasome

Introduction

IL-1 receptor (IL-1R) activation has been identified as a key participant in many rheumatic diseases. Initially approved for the treatment of rheumatoid arthritis, IL-1 blockade strategies have diversified in number and in the diseases for which they are used. This review will cover the evidence for IL-1 β blockade in rheumatic diseases with a focus on emerging indications and human data.

Conflicts of Interest

Dr. Kahlenberg has received honoraria and received research funding from Novartis.

IL-1R signaling

Two cytokines are able to stimulate IL-1R activation: IL-1 α and IL-1 β . IL-1 α is constitutively expressed by mesenchymal and epithelial cells and is released as an alarmin to signal cellular damage/necrosis or as a signal of DNA damage(1)*. IL-1 β is not constitutively expressed, but is upregulated, primarily in monocytes and macrophages, following NF κ B activation. IL-1 β is activated via cleavage by caspase-1, an enzyme which is activated when recruited to a protein scaffold termed the inflammasome. Several inflammasome complexes have been described, but those containing the scaffold NLRP3 have been the most robustly studied in rheumatic diseases. Following release of IL-1 α or IL-1 β , binding of active cytokine to the IL-1R1 then recruits the IL-1R accessory protein (IL-1RaP), initiating a signaling cascade which results in NF κ B-mediated transcription, Cox-2 induction and production of pro-inflammatory mediators such as IL-6, IL-8 and prostaglandin E2(2). Activation of these mediators results in neutrophil recruitment, fever and broadening of the inflammatory response. Endogenous regulation of signaling occurs via tight control of IL-1 α and IL-1 β activation and release as well as production of the IL-1 receptor antagonist (IL-1RA), which binds IL-1R and prevents IL-1RaP recruitment.

Therapeutic armamentarium

Medications which inhibit IL-1 signaling (see Figure 1) include FDA approved therapies and drugs in development. Three main strategies are employed: 1. Block the formation of the active receptor heterodimer. This strategy is utilized by the recombinant IL-1 receptor antagonist (IL-1RA) (anakinra), which is FDA approved for refractory rheumatoid arthritis (RA) and neonatal-onset multisystem inflammatory disease (NOMID). It is given as a daily injection in patients with normal renal function. Multimeric forms of IL-1RA with prolonged half-lives are currently being studied and show therapeutic potential in murine models of arthritis(3)*. 2. Neutralize circulating IL-1 β with a monoclonal antibody. Canakinumab is a monoclonal antibody against IL-1 β and is approved for use in systemic-onset juvenile idiopathic arthritis and CAPS. This is given as a subcutaneous injection every 8 weeks. Gevokizumab is a monoclonal antibody to IL-1 β which is also being studied in various trials. 3. Neutralize circulating IL-1 β >IL-1 α with soluble recombinant receptor. Rilonacept, which is a soluble fusion protein of the IL-1R1 and the IL-1RaP, is FDA approved for cryopyrin-associated periodic syndrome (CAPS), which include familial cold auto-inflammatory syndrome, Muckle-Wells, and NOMID. It has greater affinity for IL-1 β (versus IL-1 α) and is given as a weekly subcutaneous injection. Side effects to FDA approved anti-IL-1 medications can include injection site reactions, especially with daily anakinra, and an increased risk of infections(4). Reversible neutropenia is also occasionally noted(5). Other IL-1 inhibitory drugs are in development (reviewed in(6, 7)) and include medications which inhibit activation of the inflammasome, the molecular complex which activates IL-1 β (8). Evaluation of inhibitors of kinases downstream of the IL-1R is also under way(9, 10)*.

Treatment of autoinflammatory disease

Differentiation between autoimmune and autoinflammatory diseases relies on the development of specific adaptive immune responses in the former and lack of such immune responses in the latter. Autoinflammatory diseases are characterized by dysregulated inflammation primarily driven by monocytes and macrophages, which are robust producers of IL-1 β and other inflammatory cytokines, and are consequently excellent targets for IL-1 directed therapies.

CAPS

CAPS are the best studied group of autoinflammatory diseases and results from genetic mutations in NLRP3, the central scaffold for the inflammasome. These mutations result in increased IL-1 β activation and release. Indeed, recent data suggest that monocytes from these patients are hyperactive to inflammatory stimuli and have a defect in antioxidant upregulation which leads to increased cellular stress, decreased native IL-1Ra synthesis and thus enhanced IL-1 β release(11)**. These patients exhibit a spectrum of symptoms ranging from fever, arthritis, urticarial rash, conjunctivitis, and chronic meningitis (12, 13). Severity ranges from short episodes of fever, rash, and arthritis that are triggered by cold exposure in FCAS, to continuous fever, neurologic dysfunction, permanent organ damage and death in untreated NOMID (14, 15). Typically, presentations are during early childhood, but a recent case report suggests that adult-acquired somatic mutations in NLRP3 can also result in CAPS(16)**. All CAPS diseases respond well to IL-1 blockade, and use of these medications is now recommended as first line therapy by Single Hub and Access point for pediatric Rheumatology in Europe(17)*. Despite providing dramatic symptom relief, IL-1 blocking therapy does not improve amyloidosis in patients who develop this complication prior to initiation of IL-1 blockade therapy(18)*. Thus, early treatment before organ damage is critical for CAPS patients.

Other Periodic Fevers

Other genetic autoinflammatory diseases such as deficiency of the IL-1 receptor antagonist (DIRA), TNF receptor-associated periodic syndrome (TRAPS), Hyper IgD syndrome (HIDS), an autosomal recessive disease resulting from mutations in the gene for mevalonate kinase, and familial Mediterranean fever (FMF) all have documented responses to IL-1 blockade in the literature and their use was recently recommended for TRAPS and HIDS(17). An ongoing phase 3 trial is looking at canakinumab for these diseases (NCT02059291). DIRA has an especially good response to anakinra, as this replaces the deficient IL1RA(15, 19). Rilonacept is also being investigated for this use as well (NCT01801449). Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome is the most common cause for periodic fevers in children and may also respond to IL-1 blockade. Monocytes from PFAPA patients with active flares secrete increased IL-1 β following stimulation with LPS(20), similar to what has been noted for CAPS patients(13). Several case reports are suggestive of good disease control with IL-1 blockade(21, 22).

Schnitzler Syndrome

This rare adult-onset autoinflammatory disorder is characterized by fevers, urticarial rash, arthritis, and IgM gammopathy. Increased propensity for production of IL-1 β has been noted in these patients(23). Interestingly, somatic mosaicism for NLRP3 mutations have recently been described as a possible mechanism for disease development in some patients; peripheral blood mononuclear cells from patients with NLRP3 mosaicism had spontaneous IL-1 β production(24)*. Treatment response to anakinra is dramatic with a complete remission rate of 83% reported in one French retrospective study(25). Canakinumab has also been reported as effective in open label studies(26).

Systemic Juvenile Idiopathic Arthritis and adult-onset Still's disease (AOSD)

Systemic Juvenile Idiopathic Arthritis (sJIA) is an inflammatory arthritis associated with systemic inflammation, elevated ferritin levels, fever, evanescent rash, serositis, splenomegaly and/or lymphadenopathy. AOSD is considered to be in the spectrum of sJIA with similar symptoms but a later age of onset. Both diseases are characterized by elevated IL-1 β levels(27). Treatment with IL-1 β blockade appears to be effective in sJIA and has led to approval of canakinumab for this indication.

Macrophage activation syndrome (MAS) is a potentially fatal complication of sJIA with mortality estimates reaching 22%(28). Case reports have suggested that treatment with anakinra may benefit MAS(29). However, a recent study has noted that despite adequate disease control with canakinumab, the incidence and outcome of macrophage activation syndrome in sJIA patients is not affected by this treatment(30)**. Indeed, studies suggest that IL-18, another inflammasome activated cytokine is elevated in patients with MAS and may reflect risk of developing this complication(31)**. Further research into the relationship of IL-1 β vs. IL-1 α blockade and IL-18 activation in MAS is warranted.

Fairly robust case report data supports the use of IL-1 antagonism in AOSD (32, 33), and several ongoing trials (NCT02204293 and NCT01033656) are evaluating the efficacy of IL-1 antagonism in this disease. A recent trial has just completed evaluating the efficacy of rilonacept in which 3/5 treated patients were reported to meet an ACR20 improvement, and the mean lowering of prednisone was by 7 mg after 24 months (NCT00094900). Publication of this data has not yet been completed.

Pericarditis

Non-infectious pericarditis can be a complication of several autoimmune disorders, but idiopathic, recurrent pericarditis may also be a manifestation of autoinflammatory disorders such as FMF or TRAPS. When not associated with an identifiable disease, idiopathic recurrent pericarditis behaves like an autoinflammatory disorder characterized by recurrent bouts of chest pain, pericardial effusions and fevers(34). Scattered case reports have suggested that anakinra may be beneficial for recurrent, idiopathic pericarditis, and a recent systematic review suggested that there is a benefit to anakinra use with a tolerable side effect profile(35). An Italian randomized placebo controlled trial of anakinra in recurrent idiopathic pericarditis was recently completed (NCT02219828), and preliminary results suggest a complete response rate in 20 patients who were given anakinra and recurrent flares

in patients subjected to medication withdrawal(36). Further research into the utility of IL-1 blockade in pericarditis is warranted.

Behçet's disease

This disease is characterized by recurrent oral and genital ulcerations, pustular rashes and a high incidence of ocular inflammation. While many cytokines have been noted to play a role in this disease, IL-1 β appears to be a central player in disease pathogenesis(37). Case reports suggest that there may be some improvement in mucocutaneous features of Behçet's with IL-1 blockade, but this is usually not a complete response. Colchicine often works better for this indication and is the preferred first line therapy(37). For Behçet's-associated uveitis, which does not respond to first line agents, blockade of IL-1 pathways may be beneficial. A phase II trial of gevokizumab, a monoclonal antibody to IL-1 β , demonstrated highly effective control of ocular inflammation in patients refractory to treatment with azathioprine or cyclosporine(38). The effects of IL-1 antagonism on other manifestations of Behçet's, such as GI involvement or vasculitis, are unknown.

Uveitis

In addition to improvement in Behçet's ocular inflammation, interest surrounds treatment of refractory idiopathic uveitis with IL-1 blockade. In 2012, gevokizumab was granted orphan drug status for the treatment of resistant intermediate, posterior and panuveitis as well as chronic refractory anterior uveitis. IL-1 β levels are elevated in the aqueous of inflamed anterior chambers of HLA-27 positive patients with uveitis, and cytokine levels correlate with disease activity(39). However, the final determination for the role of IL-1 blockade in uveitis has yet to be made. A phase 3 trial evaluating ocular injection of gevokizumab for treatment of active, noninfectious uveitis was recently terminated without reporting of the data(ClinicalTrials.gov NCT01684345). Further research is needed to determine whether IL-1 blockade will be an effective addition to the treatment regimens for uveitis.

Neutrophilic skin disorders

Case reports of improvement in pustular psoriasis(40) and pyoderma gangrenosum(41) with IL-1 blockade support a role for this cytokine in their pathogenesis. A recent small randomized control trial also documented some benefit for anakinra in the treatment of hidradenitis suppurativa(42)*. Similar reports suggest efficacy for anakinra in treatment of refractory Sweet's syndrome(43, 44). Larger-scale trials should be considered to verify the utility of IL-1 blockade in these diseases.

Chronic recurrent multifocal osteomyelitis (CRMO)

CRMO is characterized by persistent, sterile inflammatory lesions of bone which result in bone resorption, swelling and pain. IL-1 β is overproduced by CRMO monocytes, and upregulation of inflammasome genes in these patients has been reported(45). Recent studies have implicated dysregulation of IL-10 as a reason for IL-1 β hyper production. Decreased IL-10 production in CRMO patients allows for enhanced inflammasome activation and IL-1 β production(46)**. A recent case series supports the blockade of IL-1 signaling for treatment of CRMO. 7/7 patients had improvement of symptoms with the use of anakinra

and 40% of bone lesions completely resolved after at least 6 months of treatment(47). Again, larger-scale trials are needed to confirm the efficacy of IL-1 antagonism for CRMO.

Treatment of Autoimmune Diseases

Rheumatoid arthritis

Affecting approximately 1% of the US population, rheumatoid arthritis is characterized by symmetric inflammation of small joint joints and an increased risk of organ inflammation. Elevated levels of inflammatory cytokines including IL-1 β , IL-6, IL-17 and TNF α (48) have been noted in the serum of RA patients, and targeting of IL-1 β was an early development in RA therapy. Anakinra received FDA approval for treatment of RA in 2001. However, the effectiveness of this medication is not as robust as other biologic therapies for this disease, and significant injection site reactions has limited its utility in RA(49). Thus, the use of anakinra has fallen to a second-line therapeutic in this disease. In 2011, a small trial demonstrated moderate efficacy for canakinumab, but further work remains to determine whether this medication would be added to RA treatment strategies(50).

RA patients have an increased risk of cardiovascular disease (reviewed in (51)), and some data suggests that certain features of this complication may be benefited by IL-1 antagonism. In a study of 80 RA patients (60 with and 20 without coronary artery disease), a single dose of anakinra has been reported to improve flow-mediated dilation in RA patients with coronary artery disease(52). Similar improvements in left ventricular function were reported in another study(53). Importantly, a case report demonstrated benefit for RA-associated heart failure following administration of anakinra(54). Further research is required to know if IL-1 blockade may be a viable option for treatment of cardiovascular comorbidities in the RA patient population.

Other autoimmune diseases

Other autoimmune diseases, such as lupus and scleroderma, have some links to IL-1 signaling, but little clinical data for IL-1 blockade in patients. For example, IL-1 α has been noted to be increased in systemic sclerosis patients(55), and anakinra has been reported to inhibit dermal contraction *in vitro*(56). The effect of anakinra on patient fibrosis is unknown. IL-1 polymorphisms have been associated to the development of lupus, but the clinical relevance of this data is lacking(57). Further, murine models suggest that IL-1 signaling may be of importance for autoimmune diseases(58), and there is very preliminary data that anakinra can benefit lupus arthritis(59). Further research is required to understand how this signaling pathway may play a role in autoimmune disease development.

Crystal arthropathies

Gout

Attacks of gouty arthritis are characterized by an intense inflammatory response driven by monosodium urate (MSU) deposition, which has been shown to stimulate inflammasome activation(60). Consequently, IL-1 antagonism is an effective, although not FDA approved, mechanism by which to quiet gout flares. Anakinra has demonstrated effectiveness(61) and

is a useful alternative to NSAIDs, colchicine or prednisone in hospitalized patients with comorbidities that prevent the use of these medications(62). Randomized, active-controlled trials of both canakinumab(63) and rilonacept(64) showed efficacy for treatment and prevention of gout flares. However, one study suggested that benefit of rilonacept was not superior to the use of indomethacin alone(65). The applications for FDA approval for canakinumab and rilonacept for treatment and prevention of gout flares were turned down secondary to risk vs. benefit analysis.

Pseudogout

Similarly to monosodium urate, calcium pyrophosphate dehydrate (CPPD) crystals stimulate inflammasome activation and subsequent IL-1 β release(60). Case reports suggest that anakinra is an effective way to treat refractory and widespread pseudogout flares(66, 67). It is likely that anakinra will also find a place in pseudogout treatment similar to its specialized role in complicated gout patients.

Cost of therapy

IL-1 blockade strategies are proving to be an effective therapy with a low side effect profile for many diseases. A major drawback of the widespread use of these medications is the cost: some formulations costing as much as \$16,000 per dose (www.ahdonline.com/select-drug-updates/1468-article-1468). As the indications for IL-1 blockade expand, cost-benefit analysis will need to be completed to understand how the utility of these drugs can be maximized. Alternatively, research into the development of lower-cost IL-1 antagonism methods should be pursued.

Conclusion

IL-1 signaling is a central regulator for many auto-inflammatory and some autoimmune diseases. Novel uses for blockade of this pathway will likely continue to accumulate, and clinical response to such inhibition will also help to identify new pathologic pathways which do or do not involve IL-1R activation. Ongoing trials for common and rare disease indications will likely strengthen the push to use these medications in clinic. IL-1 inhibition may nearly function as an anti-inflammatory panacea, but evaluation of the cost of therapy- in terms of medication risk and effects on the cost of health care- will be essential to its widespread clinical utility.

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Abbreviations

AOSD	adult-onset Still's disease
CAPS	cryopyrin associated periodic fever syndromes

DIRA	deficiency of the interleukin-1 receptor antagonist
FMF	familial Mediterranean fever
HIDS	hyper IgD syndrome
IL-1	interleukin 1
IL-1R	IL-1 receptor
IL-1RA	IL-1 receptor antagonist
IL-1RaP	IL-1R accessory protein
MAS	macrophage activation syndrome
NOMID	neonatal-onset multisystem inflammatory disease
PFAPA	Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis
TRAPS	TNF receptor-associated periodic syndrome

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Key Points

- IL-1 signaling is a common pathway for inflammation activation in a wide variety of rheumatic diseases.
- IL-1 blockade is an effective treatment for many inflammatory disorders where IL-1 levels have been reported to be elevated.
- While side effects of IL-1 blockade medications are generally tolerable, the cost of the medication and risk of infection need to be weighed against other alternative treatment options.

Figure 1. Drugs that antagonize IL-1 signaling utilize various approaches to block activation of the IL-1R by IL-1 α and IL-1 β

Anakinra binds to the IL-1R1 thus preventing recruitment of IL-1R accessory protein (IL-1RaP), a step which is required for activation of downstream signaling cascades. Because it interacts with the receptor, anakinra inhibits both IL-1 α and IL-1 β signaling. Canakinumab and gevokizumab are both monoclonal antibodies which recognize IL-1 β and prevent its binding to the receptor. These drugs have no effect on IL-1 α signaling. Rilonacept is a fusion protein between the IL1R1 and IL1RaP linked to the Fc portion of human IgG1. This medication has a much higher affinity for IL-1 β than IL-1 α and thus antagonizes IL-1 β -mediated signaling more effectively.