Interleukin-1β Targeted Therapy in Severe Persistent Asthma (SPA) and Chronic Obstructive Pulmonary Disease (COPD): Proposed Similarities between Biphasic Pathobiology of SPA/COPD and Ischemia-Reperfusion Injury

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Abstract

The histopathology of severe persistent asthma and chronic obstructive pulmonary disease is predominantly characterized by neutrophilic inflammation. It is posited that chronic hypoxia from hypoventilation in combination with hypoperfusion and hypercapnia are associated with induction of pulmonary tissue acidosis in SPA and COPD, which in turn provide ideal conditions to induce danger-associated molecular patterns, i.e., crystallized and calcium pyrophosphate. These stimuli in combination with other danger-related biochemical signals are capable of stimulating an innate immune receptor (cryopyrin inflammasome, NALP3) and cause interleukin-1β secretion with subsequent neutrophilic inflammation. There is evidence to suggest that the mechanisms and pathobiology associated with chronic hypoxia, reduced perfusion and reoxygenation in SPA/COPD may exhibit similarities to the biphasic pathobiology involved in ischemia-reperfusion injury. A rationale is suggested for trials of IL-1β targeted therapies as an adjunct strategy to control neutrophilic inflammation in these conditions.

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Bronchial asthma is a heterogeneous inflammatory disorder of the bronchial airways that is mediated by activated eosinophils. Evidence supporting this concept includes responsiveness to corticosteroids in the majority of asthmatics with attenuation of eosinophilic inflammation. However, the central role of eosinophils in severe persistent asthma has been contested by data from anti-interleukin-5 monoclonal antibody trials [1] that demonstrated reduction of eosinophilic inflammation without improvement in asthma symptomatology. About 10% of asthmatics are refractory to corticosteroid therapy and many of these patients exhibit neutrophilic and/or a combination of neutrophilic and eosinophilic inflammation. Observations from a murine model of steroid-resistant asthma with neutrophilic inflammation indicated that treatment with dexamethasone was associated with an increased number of neutrophils in lung tissue and unchanged numbers of macrophages in broncho-alveolar lavage fluid [2]. Wenzel et al. [3] provided evidence of high neutrophil counts in bronchoalveolar lavage fluid and bronchial biopsies (endo, trans) obtained from corticosteroid-resistant severe asthmatics. Likewise, patients with chronic obstructive pulmonary disease exhibit predominantly neutrophilic inflammation and are generally refractory to beneficial effects of corticosteroids. Consequently, accumulating evidence suggests that neutrophilic inflammation may be of significant importance in both conditions. In particular, SPA [4] is frequently characterized by minimal atopy with low levels of immunoglobulin E, late onset in life, chronic airflow obstruction with labile symptomatology, and resistance to high dose corticosteroid therapy [5]. Traditionally, both conditions are difficult to treat and are associated with high rates of morbidity, medical interventions, health costs, and death.

IL-1 family, neglected mediators of neutrophilic inflammation in SPA and COPD

SPA and COPD have been extensively studied and there appear to be many interactive molecular events involved in the pathobiology of these conditions. Several reviews [5,6] have identified molecular targets to potentially control neutrophilic inflammation, such as neutrophilic chemotactic factors (leukotriene B4, anaphylatoxins C3a and C5a, IL-6, IL-8, IL-17A, and tumor necrosis factor-alpha), epithelial growth factor receptor, activated adhesion molecules (integrins, selectins), growth factors (granulocyte macrophage-colony stimulating factor), and signal transduction/transcription pathways (nuclear factor-κ β, MAP kinases). Surprisingly, the role of IL-1 family members (IL-1β, IL-1α, IL-18, IL-1R) as potential mediators of neutrophilic inflammation in SPA/COPD was not mentioned in the cited reviews. A primary purpose of the present review is to emphasize the involvement of IL-1β in the pathobiology of these pulmonary disorders based on new information involving innate immune mechanisms that stimulate IL-β secretion and in turn induce neutrophilic inflammation [7].

This discussion will focus on IL-β as the prominent member of the IL-1 family that causes neutrophilic inflammation. IL-1α and IL-1β are isoforms with similar biological activity, and both require IL-1R for expression of their biological activity, such as neutrophilic influx that can be neutralized with IL-1R antagonists. There are conflicting data regarding the role of IL-18 as a mediator of neutrophilic inflammation in pulmonary disorders. IL-18 was

SPA = severe persistent asthma
COPD = chronic obstructive pulmonary disease
IL = interleukin

not detected in a murine model of bleomycin-induced neutrophilic lung inflammation that was shown to be primarily mediated by IL-1β [8]. Additionally, neutrophilic inflammation was not reduced in IL-18 receptor knockout mice [8]. In contrast, a murine asthma model [9] induced by ovalalbumin demonstrated a reduction of early neutrophil influx in BALF following ovalalbumin challenge if mice were pretreated with anti-IL-18 or IL-1ra, suggesting mediation by IL-1β and IL-18. These different results may reflect varied biological actions of IL-18 depending on the type of experimental model as well as intrinsic biological differences between IL-18 and IL-1β [10]. However, there is apparent redundancy in the IL-1 family suggesting that IL-18 may also mediate neutrophilic inflammation. Nevertheless, this article will primarily focus on IL-1β since the evidence is more substantial and compelling regarding its role inducing pulmonary neutrophilic inflammation.

Innate immune mechanisms capable of inducing IL-1β secretion

It is known that IL-1β secretion from mononuclear cells can occur by microbial pathogen-associated molecular pattern stimulation of innate immune receptors, namely the cytoplasmic cryopyrin (NALP-3), NALP-1 and Ipaf inflammasomes, and cell membrane toll-like receptors. PAMPs can also stimulate TLRs 2 and 4 to secrete TNFα, which in turn can increase transcription of pro-inflammatory IL-1 genes and subsequent IL-1 α/β production. All these and other pathways, such as host-derived RNA and DNA stimulation, can cause secretion of IL-1β [7]. In addition, a new important pathway for IL-1β secretion was recognized from the discovery of the cryopyrin inflammasome (NALP-3) by Hoffman et al. [11] and Martinon et al. [12] who investigated hereditary cryopyrin auto-inflammatory periodic fever syndromes, and from *in vitro* data gathered by other investigators [13,14]. The combined studies demonstrated that IL-1β secretion can occur from stimulation of the cryopyrin inflammasome and TLRs 2 and 4 by danger-associated molecular patterns, i.e., crystals of uric acid and calcium pyrophosphate. The cryopyrin inflammasome is now considered to be an innate immune sentinel located in the cytoplasm of monocytes and neutrophils that can detect the presence of many diverse danger signals, such as intrinsic particulates (cUA, cCaPP), extrinsic particulates (asbestos, silica, toxins, alum) [15], and varied biochemical signals, which in turn induce pro-inflammatory responses by secretion of IL-1β.

Proposed pathobiology causing DAMPs formation in SPA/COPD

SPA/COPD exhibit hypoxic tissue environments, primarily due to impaired ventilation from mucus inspissation, reduced airway caliber and regional atelectasis. It has also been observed that hypoperfusion causes pulmonary tissue hypoxia. Harris and co-workers [16], using positron emission tomography in asthmatics with bronchoconstriction induced by methacholine challenges, observed reduced pulmonary perfusion in localized hypoventilated regions. Abnormal Va/Q ratios in regions with hypoventilation revealed hypoxemia with calculated PaO_2 levels of less than 50 mmHg, caused by hypoxic reflex pulmonary vasoconstriction due to hypoventilation. Freyschuss et al. [17] reported on hypoxemia associated with exercise-induced asthma. Abnormal V/Q ratios during bronchospasm from exercise were attributed to a mixture of hypoperfusion in hypoventilated regions and hyperinflation impeding blood flow in other pulmonary locations. Consequently, chronic hypoxia in SPA/COPD is likely caused by a combination of ventilation impairment and hypoperfusion, which is essentially ischemia in this setting.

Numerous studies have demonstrated that hypoxia caused by ischemia in other organ systems can induce anaerobic metabolism with intracellular and tissue metabolic acidosis from a combination of lactic acidosis, release of hydrogen ions from hydrolysis of ATP and accumulation of CO_2 [18,19]. Ischemic-induced hypoxia lasting just 2 minutes is known to cause a pH decrease of several logarithms. Hypoxia induced by the combination of hypoventilation and hypoperfusion in SPA/COPD is likely to cause focal anaerobic metabolism and subsequent acidosis. Support for the presence of acidosis in hypoxic pulmonary tissues is based on studies by Hunt et al. [20], who described endogenous bronchial airway acidification with pH measurements in the range of 5–6 for symptomatic asthmatics as compared to 7–8 in normal individuals. Similar findings of airway acidification have been observed in COPD in which pH values were lower compared to normal (controls) – 7.16 mean value for COPD vs. 7.43 mean value controls [21] and 6.97 mean value for COPD vs. 7.6 mean value controls [22]. It appears that acidic conditions exist in SPA/COPD, providing ideal conditions for crystallization of cUA and cCaPP, as crystallization and insolubility of UA increase inversely with pH and CaPP can crystallize optimally in a pH range of 6–7 [23]. Consequently, it is posited that formation of DAMPs is likely in SPA/COPD, which could cause secretion of IL-1β by stimulation of the cryopyrin inflammasome.

Other danger-associated biochemical signals associated with hypoxia and acidosis may occur in these pulmonary conditions. Reduced pH can disrupt cell mitochondrial ATP production, creating alterations in ion channels and membrane dissolution. This can result in intracellular sodium and calcium ion influx with intracellular hypotonic stress, potassium ion efflux and subsequent intracellular hypokalemia, which is another powerful inducer of IL-1β secretion by the cryopyrin inflammasome. In addition, free ATP from cytotoxic injury can activate purinergic P2X receptors and cause further efflux of potassium ions. Reactive oxygen species can be formed during phagocytosis of cUA and in turn stimulate secretion of IL-1β [15] via the cryopyrin inflammasome. The concentrations of UA may increase due to the combination of xanthine oxidase activation by hypoxia and low pH, and from purine catabolism in stressed and dying cells. Higher concentration leads to super-saturation causing spontane-

BALF = broncho-alveolar lavage fluid
PAMP = pathogen-associated molecular pattern
TLR = toll-like receptor
TNFα = tumor necrosis factor-alpha
cUA = crystals of uric acid
cCAPP = crystals of calcium pyrophosphate
DAMP = danger-associated molecular pattern
UA = uric acid

ous crystallization, especially at low pH [23], which provides increased cUA mass for cryopyrin inflammasome stimulation. Pyrophosphates, which are derived from ATP degradation, can combine with higher intracellular calcium ion concentration to form calcium pyrophosphates that can crystallize at low pH and stimulate secretion of IL-1β by the cryopyrin inflammasome. Moreover, ATP released from cytotoxic injury can bind directly to cryopyrin, which has ATPase activity that can further induce hydrolysis of ATP to pyrophosphates. Consequently, conditions of hypoxia, hypercapnia, focal hypoperfusion and pulmonary tissue acidification circumstantially support the posited hypothesis that danger signals may be formed – i.e., cUA/cCaPP [13,14], ATP-dependent activation of the purinergic P2x receptor causing intracellular hypokalemia, ROS [15] in SPA/COPD and cause secretion of IL-1β by stimulation of the cryopyrin inflammasome and to some extent TLRs 2 and 4.

Evidence for presence of UA in human lung

As previously described, a fundamental part of the posited hypothesis is that pulmonary neutrophil inflammation can be indirectly caused by an increase in DAMPs, particularly UA. A review of the literature reveals no reports of UA measurements in lung tissue specimens from patients with SPA/COPD. However, several investigators detected UA in BALF of humans and suggested it functions as an antioxidant to neutralize airborne oxidants, such as nitrogen oxides, ozone and oxidants trapped in cigarette smoke. Slade et al. [24] measured antioxidants in BALF from 13 healthy volunteers aged 18 to 35 years with no history of allergy, asthma, acute or chronic respiratory disease or cardiac disorder, and found a mean UA concentration of 15.88 nanomoles/mg protein. Crissman et al. [25] demonstrated higher UA in BALF of smokers (206 ng/ml) vs. non-smokers who were healthy volunteers (146 ng/ml). Yigla and team [26] reported increased UA concentration in BALF from COPD patients who smoked (mean 0.85 mg/dl or 5.3 mmoles/L) compared to subjects without COPD who smoked (mean 0.45 mg/dl or 2.8 mmoles/L). Furthermore, Kelly et al. [27] demonstrated elevated UA in BALF of asthmatics. It is of special interest that increased UA in BALF has been shown to be associated with increased UA concentration in the lung tissue of an animal model exposed to ozone. In summary, these studies suggest that uric acid is one of several antioxidants present in human BALF that can increase in response to inhaled oxidants, such as cigarette smoke. They also support the concept that increased UA formation may occur in COPD and asthma, lending credence to the possibility of increased UA in hypoxic-acidic neutrophilic pulmonary conditions.

UA's function as an antioxidant to neutralize intrinsic and extrinsic ROS

It has been proposed that UA in lungs of humans functions as an antioxidant to neutralize environmental oxidants, such as ozone, nitric oxides and oxidants in cigarette smoke [24,28]. In addition, there are animal data [29] supporting the concept that UA represents one of several antioxidants present in BALF that neutralize ROS formed during hypoxic/ischemic conditions and during oxygenation. Schmidt and co-workers [29], using an *ex vivo* model of rabbit lungs, demonstrated that UA concentrations in BALF increased over time during ischemia in combination with either anoxia or hyperoxia. Extrapolation of these data to SPA/COPD is obviously difficult, although it is probable that anoxia would be present in atelectatic regions and hyperoxia could occur in regions of improved ventilation from therapeutic interventions involving oxygen administration, bronchodilators, corticosteroids, etc. Nevertheless, if anoxia and/or hyperoxia and possibly even hypoxia exist in areas of reduced or absent perfusion (i.e., ischemia), it would be reasonable to speculate that elevated UA concentrations may occur in SPA/COPD during those conditions. This concept fits with the posited pathobiology of SPA/COPD that tissue and cell damage from hypoxia-induced acidosis can result in increased DAMPs formation, particularly cUA.

Detection of IL-1β in SPA and COPD

In order to posit the involvement of IL-1β in induction of neutrophilic inflammation in SPA/COPD, its presence in these conditions needs to be demonstrated. Borish et al. [30] observed elevated IL-1β in BALF samples obtained from patients with asthma. Brasier and associates [31] investigated SPA cytokine profiles in BALF from patients with mild to severe asthma. Markedly reduced levels of IL-1β receptor agonist were observed in the severe asthma phenotype, suggesting enhanced IL-1β signaling. Tonnel et al. [32] presented evidence of markedly elevated IL-1β along with other cytokines in BALF from patients with status asthmaticus. Chung et al. [33] demonstrated the presence of IL-1β in COPD, and Gessner et al. [34] noted increased IL-1β in exhaled breath condensates of COPD patients as compared to normal volunteers. Although other cytokines were elevated in both conditions, the presence of IL-1β is important as it provides a trail of evidence for its involvement as a potential mediator of neutrophilic inflammation in these pulmonary disorders.

Evidence that IL-1β may induce neutrophilic inflammation and remodeling in SPA/COPD

Results from an animal model support the notion that IL-1β can cause pulmonary neutrophilic inflammation. Lappalainen and team [35] studied transgenic mice with human IL-1β expression in lung epithelium. Induction of IL-1β secretion in murine lungs caused pulmonary inflammation characterized by neutrophil and macrophage infiltrates. The histopathology included elastin fiber disruption, fibrosis in airway walls with increased thickness of conducting airways, and enhanced mucin production, all features of SPA and COPD pathobiology.

Ample studies support the relationship between IL-1β-induced cascade of pro-inflammatory events [36] and neutrophilic inflammation, such as up-regulation of vascular adhesion molecules, IL-6, IL-8 and IL-17A release, increased neutrophil and monocyte chemokines (MCP-1), stimulation of phospholipase-A_2 activation, and prostaglandin E release.

In addition, there are specific immune and biochemical path-

ROS = reactive oxygen species

ways that can contribute to neutrophilic inflammation in SPA/COPD, such as:

- Stimulation of innate immune receptors by microbes/PAMPs in combination with DAMPs can cause synergistic secretion of IL-1β with subsequent amplification of neutrophilic inflammation. The likelihood of this synergism involving SPA/COPD is considerable, as microbial infections are commonly associated with these conditions.
- Dostert et al. [15] provided evidence that cytoplasmic phagocytosis of cUA, asbestos particles, and silica can activate NADPH oxidase with generation of ROS, which in turn stimulate the cryopyrin inflammasome to secrete IL-1β. The obvious import of these observations is that generated ROS can induce IL-1β secretion as well as leak extracellularly to cause direct cell damage and subsequent neutrophilic inflammatory necrosis.
- IL-1β and other chemotactic stimuli can cause an influx of neutrophils that may disintegrate at low pH environment and release lysozymes (i.e., elastase), causing further damage to tissues.
- Experimental asthma studies indicate that IL-1β can induce differentiation of Th17 cells with secretion of IL-17A that induces pulmonary neutrophilic inflammation [37].
- Results of exhaled breath condensates from cigarette smokers have demonstrated elevated IL-6 and leukotriene B4, indicating a correlation between these chemotactic factors and induction of neutrophilic inflammation in smokers. IL-6 is induced by IL-1β stimulation, suggesting that the latter has a primary influence in causing neutrophilic inflammation in lungs of smokers.
- Data suggest that induction of IL-8 (CXCL-8) can be synergized by the combined action of IL-17 and IL-1β on human airway smooth muscle and cause increased neutrophil mobilization, hyper-responsiveness of the airways and remodeling in asthma [38]. Increased IL-8 secretion is also common in the pathobiology of COPD.
- Evidence exists that IL-1β can orchestrate pro-fibrotic and remodeling events by enhancing fibrosis [8], possibly by synthesis of hyaluronan [39] and by amplification of IL-13 up-regulation of platelet-derived growth factor that can stimulate growth of lung fibroblasts.

Inflammasome activation, IL-1β secretion and induction of pulmonary neutrophilic inflammation

In a unique murine model of bleomycin-induced lung injury, Gasse et al. [8] demonstrated that IL-1β secretion caused neutrophilic chemokine/cytokine (i.e., KC and IL-6) production and subsequent neutrophilic inflammation with remodeling and fibrosis. The study also provided conclusive evidence that IL-18 and TLRs were not involved as a cause of this pathobiology.

Additionally, the study demonstrated that IL-1β secretion and neutrophilic inflammation were dependent on the presence of the ASC adaptor protein, as ASC knockout mice exhibited no neutrophilic inflammation or IL-1β secretion. ASC is an essential adaptor protein involved in oligomerization and activation of intracellular multi-protein complexes to form cytoplasmic inflammasomes (NALP-1, NALP-2, NALP-3, and Ipaf), which require ASC for their function. All but NALP-2 are stimulated by PAMPs and only NALP-3 is stimulated by DAMPs. Stimulation of inflammasomes in turn activate caspase-1 to convert stored pro-IL-1β to Il-1β that is then secreted from phagocytic cells. The investigators stated that "bleomycin-induced cell injury resulted in the release and sensing of DAMPs by the inflammasome." Based on this statement from the study authors, it would appear that cryopyrin NALP-3 was involved in this model since it is the only ASC-dependent inflammasome activated by DAMPs for IL-1β secretion. The type of DAMPs involved in this model was not established in the study. However, it is known that bleomycin is a chemotherapeutic agent that interferes in DNA/RNA synthesis and can cause tumor lysis with degradation of purines and increased formation. Based on this information, UA [10] would likely be one of the DAMPs that could stimulate NALP-3. This investigative model serves as an important template for pulmonary neutrophilic inflammation that may be applicable to SPA/COPD and other pulmonary neutrophilic inflammatory disorders as it demonstrated the likely relationship between activation of NALP-3 inflammasome by DAMPs, i.e., cUA, followed by IL-1β secretion and subsequent neutrophilic inflammation. Further validation in animal models of SPA/COPD is warranted.

Parallels between biphasic pathobiology of SPA/COPD and ischemia-reperfusion injury

Based on composite data from several sources [Table 1] it is suggested that the phase of hypoventilation/hypoperfusion [29] with hypoxic-acidosis in SPA/COPD causes increased formation of DAMPs (cUA), ROS, and IL-1β with subsequent neutrophilia. It is further suggested that similar pathobiology occurs during the re-oxygenation phase based on animal studies [29] in which increased UA production occurred during hyperoxia in combination with hypoperfusion (ischemia), conditions that are likely present in SPA/COPD. Several investigators have speculated that increased UA formation is a homeostatic response to intrinsic

Table I. Similarities between biphasic pathobiology of pulmonary neutrophilic inflammation and ischemia-reperfusion injury

	Pulmonary neutrophilic inflammation	Ischemia-reperfusion injury
Hypoxia	Yes [16,17]	Yes [7]
Acidosis	Yes [20–22]	Yes [7,19]
DAMPs, cUA formation	Probable [8,23-29]	Probable [7]
Inflammasome stimulation-NALP-3	Probable [8]	Unknown, but probable [7]
Evidence of biphasic inflammation (increased UA & neutrophilic inflammation)	Yes [2,8,26-29]	Yes [2,7,41]
During hypoxia	Yes [26-29,31,32]	Yes [7,41]
During re-oxygenation with resistance to treatment	Yes [2,28,40]	Yes (during reperfusion) [7,41]
Neutrophilic inflammation	Yes [2-4]	Yes [7]

Numbers represent citations

ROS formed during phases of hypoxic acidic stress and during re-oxygenation [24-29]. Increased UA formed during both phases can transform into particulate urates in low pH conditions, and with other DAMPs from cell damage cause increased ROS formation, NALP-3 inflammasome stimulation, IL-1β secretion and progressive neutrophilic inflammation. Thus it is posited that there are biphasic recurring pathobiological cycles characteristic of pulmonary neutrophilic inflammation, which may partially explain slow responsiveness to treatment with oxygen supplementation, bronchodilators, and corticosteroids [3] in SPA and COPD. Supporting this concept is the likelihood of hypoventilation/hypoperfusion with hypoxic acidosis in SPA/COPD, which can cause increased formation of DAMPs, particularly UA. Increased UA has been demonstrated in BALF from COPD subjects [26], and in BALF from mild asthmatics [27]. Hyperoxic conditions from high concentrations of administered oxygen in acutely ill asthmatics and in severe COPD [40] can cause deteriorating gas exchange and worsening symptomatology. Traditionally, the explanation for clinical deterioration by oxygen supplementation has been dampening of hypoxic respiratory drive. However, other mechanisms may be involved as there is evidence that oxygen supplementation can increase ventilation-perfusion mismatch. This could cause localized regions of hypoperfusion with hyperoxia, conditions likely to stimulate UA formation and subsequent neutrophilic inflammation.

Further support is based on observations from the murine model of Gasse et al [8], which indicates that bleomycin-induced pulmonary neutrophilic inflammation is caused by IL-1β secretion. Humans treated with bleomycin often experience lung disease from this medication and they are at high risk of progressive lung inflammation following oxygen supplementation during anesthesia. Based on the posited hypothesis, progressive neutrophilic inflammation could evolve from hyperoxia due to oxygen supplementation during anesthesia, and cause increased ROS, UA and IL-1β secretion. If this is validated, use of preoperative allopurinol or even IL-1β targeted therapy could potentially reduce or even prevent postoperative lung injury in bleomycin-treated patients.

The posited mechanisms for neutrophilic pulmonary conditions, such as SPA/COPD and bleomycin lung injury, have many similarities to those observed and proposed in ischemia-reperfusion syndromes [7]. Several ischemia-reperfusion injury models involving multi-organ systems (pulmonary, cardiac, brain, renal) [7,41] have demonstrated similar biphasic pathobiology with neutrophilic inflammation, characterized by a first phase during ischemia from hypoxia-induced acidosis and a second phase during reperfusion (i.e., reoxygenation). Causes for paradoxical increased neutrophilic inflammation during reperfusion remain unproven, but one hypothesis suggests it is caused by increased ROS from improved oxygenation and from microvascular plugging by stagnant neutrophils and platelets that cause focal ischemic hypoxic acidosis, DAMPs formation, activation of NALP3 inflammasome and more IL-1β secretion [7]. The biphasic pathobiology of ischemia-reperfusion injury has many similarities with neutrophilic pulmonary conditions, suggesting that the latter may represent an atypical form of ischemia-reperfusion injury.

IL-1β targeted therapy in animal models and in SPA/COPD

A review of the literature does not reveal trials with biologic IL-1β targeted therapy (anakinra, IL-1 TRAP) in patients with asthma of all severity levels. There is one ongoing study involving COPD sponsored by a pharmaceutical company but results are not currently available to the public. One animal study [42] used a recombinant human IL-1 receptor antagonist in rat and guinea pig models of allergic asthma. This molecule was administered by ultrasonic spraying with a reported 94.3% bioavailability via the intratracheal route. The investigators reported attenuation of asthmatic symptoms (cough, wheezing, rapid breathing, nodding, jumping and tumbling) following ovalbumin challenge to ovalbumin-sensitized guinea pigs that were pretreated with rhIL-ra. Objective data, namely down-regulation of sICAM-1 and P-selectin expression in the rhIL-ra pretreated guinea pigs, were consistent with the symptomatic improvement of the rhIL-1ra treated animals.

Anakinra and IL-1β TRAP treatment of syndromes characterized by neutrophilic inflammation, such as cryopyrin auto-inflammatory periodic fever syndromes, Schnitzler's syndrome, Still's disease and gout, have been effective with minimal serious adverse events [7]. Despite these results, the lack of respiratory trials with IL-1β targeted therapy reflects the current pharmacological focus on other biologicals, such as TNFα. Recently there has been a resurgence of interest in IL-1β targeted therapy due to commercial availability of Kineret®, i.e., anakinra (IL-1 receptor blocker), and Rilonacept® (IL-1 TRAP).

Summary

The experimental evidence supporting the proposed similarities between the biphasic pathobiology of neutrophilic inflammatory pulmonary disorders and ischemia-reperfusion injury is based on a composite of data from varied sources. The author recognizes that the evidence is not entirely conclusive but suggests there are compelling similarities to encourage validation of this observation. Hopefully the posited hypothesis involving IL-1β secretion will encourage trials of IL-1β targeted therapy in chronic pulmonary neutrophilic inflammatory conditions, particularly in corticosteroid-resistant SPA/COPD. The author recognizes that the pathobiological mechanisms involved in SPA/COPD are complex, multiple and interactive and there is a low likelihood that interference in one molecular pathway will be pivotal enough to attenuate all symptomatology. Nevertheless, there is ample evidence to recommend IL-1β targeted therapy as an adjunct treatment in combination with established controller medications.

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rhIL-ra = recombinant human IL-1 receptor antagonist

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