Targeting cytokines in inflammatory diseases: focus on interleukin-1-mediated autoinflammation

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Abstract

In this commentary, we summarize the most recent advances in the cytokine-targeting therapies. We focus on new aspects of interleukin-1 (IL-1)-mediated autoinflammation and novel strategies to target IL-1.

Introduction and context

The treatment of the broad and heterogeneous group of inflammatory diseases has been revolutionized with the introduction of therapies that target cytokines [1]. Since 1998, the year that tumor necrosis factor-alpha (TNF-α) blockade was first approved for rheumatoid arthritis (RA), our cytokine-targeting armamentarium has been enriched [1]. Table 1 summarizes all of the anti-cytokine regimens approved by the US Food and Drug Administration (FDA), and Table 2 lists the cytokine-targeting therapies that are still under investigation [2]. Recent evidence suggests that interleukin-6 (IL-6) blockade using tocilizumab is effective in RA [3] and that the p40 neutralizing antibody ustekinumab (targeting both IL-12 and IL-23) is beneficial for psoriasis [4].

Despite all of these breakthroughs in targeting cytokines, the treatment of inflammatory diseases is still imperfect and challenging. The high cost and the treatment-related adverse events (mainly infections and the reported, but controversial, increased risk for malignancies) are major drawbacks of cytokine targeting [5-7]. In addition, the available cytokine blockade is not always effective, as exemplified by the failure of the anti-p40 monoclonal antibody to show a significant benefit in patients with multiple sclerosis [8]. Furthermore, approximately 30% of RA patients do not respond adequately to anti-TNF-α treatments [9] and the IL-1 inhibitor anakinra appears to be only moderately effective in its FDA-approved indication for RA in clinical practice [5].

Although anakinra did not fulfill all of the expectations for managing RA, this therapeutic showed remarkable effectiveness in a heterogeneous group of heritable and sporadic disorders now considered IL-1-mediated autoinflammatory diseases [10]. The prototype of these diseases is the cryopyrin-associated periodic syndrome (CAPS) [11]. CAPS is now considered a continuum of one disorder with varying severity and includes the mild phenotype known as familial cold autoinflammatory syndrome (FCAS), the intermediate Muckle-Wells syndrome (MWS), and the severe form of neonatal-onset multisystem inflammatory disorder (also called chronic infantile neurologic cutaneous and articular syndrome) [11].

The immune system discriminates self from nonself and distinguishes pathogens from commensal organisms and specifically eliminates pathogens. Regulation of immune responses restrains concurrent tissue damage and orchestrates tissue repair. This balance between defense and protection of tissue integrity results from a tight regulation of the innate and adaptive branches of the immune system. Failure of these regulatory mechanisms causes an aberrant immune response ranging from inadequate defense to uncontrolled/unprovoked
infection, autoreactive lymphocytes, and high titers of autoantibodies [11,13,14]. To distinguish this group of diseases from autoimmune diseases, emphasizing the primary role of innate immunity in driving their pathogenesis, the term ‘autoinflammatory diseases’ has been proposed [11,13,14]. The new aspects in the concept of IL-1-mediated autoinflammation and the recent advances in targeting IL-1 will be the focus of this commentary.

### Major recent advances

#### Understanding Horror autoinflammaticus

More than 60 mutations in the CIAS1 gene are responsible for a hyperactive NALP3 (cryopyrin) leading to CAPS [11]. NALP3 functions as a sensor of pathogens and danger signals and is expressed mainly in immune cells, chondrocytes, and epithelial cells [15]. Upon activation, NALP3 recruits ASC (apoptosis-associated speck-like protein containing caspase-recruitment domain), Cardinal, and pro-caspase-1, assembling a multimeric complex called the inflammasome. NALP3 inflammasomes activate the downstream caspase-1, the protease that cleaves pro-IL-1, releasing the potent pyrogen IL-13 [15,16]. The understanding of the direct role of NALP3 in IL-1 processing led to the concept that CAPS (a result of hyperactive inflammasome due to mutated NALP3) is an IL-1-mediated autoinflammatory disease, justifying the use of IL-1 blockade to control disease activity [11].

### Targeting IL-1β to treat autoinflammation

The recombinant human IL-1 receptor antagonist anakinra was the first IL-1-targeting intervention used in patients with CAPS with impressive effectiveness [17-19]. The short half-life of anakinra necessitates daily injections for efficient responses, and injection site reactions are commonly observed [5,17-19]. To overcome these limitations, sophisticated investigation resulted in new efficient strategies to target IL-1 with improved pharmacokinetics and thus better compliance and tolerance [20,21].

Rilonacept is a new IL-1 blocker that functions as an IL-1 trap, binding IL-1 with an affinity at least 100-fold higher than that of the native IL-1 cell surface receptor complex [22]. Normally, IL-1β binds first to IL-1RI on the surface of target cells and subsequently IL-1 accessory protein (IL-1AcP) is recruited, thus forming a trimolecular signaling complex [16]. Rilonacept is an artificial molecule that contains the ligand-binding portions of both IL-1RI and IL-1AcP fused to a dimeric molecule containing the Fc segment of IgG1 (human immunoglobulin G1) [22]. In contrast to the daily injected anakinra, rilonacept has a half-life of approximately 7 days and thus is administered once weekly [20].
In February 2008, rilonacept (Arcalyst™; Regeneron Pharmaceuticals, Inc, Tarrytown, NY, USA) was approved by the FDA for the treatment of CAPS. IL-1 trap was proven very effective and safe in a small open-label pilot study [23] and in a larger two-part phase III clinical trial [24] which included patients with FCAS and MWS. Rilonacept not only rapidly improved patients’ symptoms, but also reduced serum levels of serum amyloid A (SAA) [20,24]. The latter is of great importance given that high serum levels of SAA are directly related to the risk of developing secondary amyloidosis [25], the main cause of renal insufficiency in these patients. Injection site reactions and upper respiratory tract infections were the two most commonly observed adverse events in patients treated with rilonacept [20].

A third IL-1 blocker, the monoclonal human anti-IL-1β canakinumab (ACZ885), was used in patients with CAPS in one small study [26] and a second recently reported randomized placebo-control clinical trial [27]. Canakinumab was administered subcutaneously once every 8 weeks and induced a remarkable clinical response with normalization of SAA and C-reactive protein levels [27]. During the treatment period, only two serious adverse events were observed: one case of urosepsis and an episode of vertigo [27].

| Targeted cytokine | Description | Investigational trials |
|------------------|-------------|------------------------|
| IL-1             | Rilonacept  | IL-1 trap (Table 1)    |
| IL-1             | Canakinumab | Anti-IL-1 Mab          |
| IL-4 and IL-13   | Pascolizumab| Anti-IL-4 Mab          |
| IL-5             | Pitrakinra (blocks IL-4 and IL-13) | Mutated IL-4 |
| IL-5             | CAT-354, IMA-638, QAX576 | Anti-IL-5 Mabs |
| IL-5             | Mepolizumab | Anti-IL-5 Mab          |
| IL-5             | MEDI-563    | Anti-IL-5 Mab          |
| IL-6             | Tocilizumab | Anti-IL-6R Mab         |
| IL-9             | MEDI-528    | Anti-IL-9 Mab          |
| IL-15            | Ustekinumab (CNTO 1275) | hlgG1 anti-p40 Mab |
| IL-15            | ABT-874/695 | hlgG1 \ anti-p40 Mab   |
| IL-17A           | HuMax-IL-15 (AMG 714) | Anti-IL-15 Mab |
| IL-23            | AIN457      | Anti-IL-17A Mab        |
| TGF-β3           | CAT-192     | Anti-TGF-beta1 Mab     |
| TGF-β3           | TFN superfamily | Ligand-binding portion of TACI fused with hlgG1 Fc |
| 1. BAFF(BLyS)/APRIL | Atacicept (blocks BlyS and APRIL) | Anti-BlyS Mab  |
| 2. LTα1/2 and LIGHT | Baminercept | Ligand-binding portion of LT-β1 R fused with hlgG1 Fc |
| 3. RANKL         | Denosumab   | Anti-RANKL Mab         |
| 4. IFN-α        | MEDI-545    | Anti-IFN-α Mab         |

For further information, see [2]. AOSD, adult-onset Still’s disease; APRIL, a proliferation-inducing ligand; ASp, ankylosing spondylitis; BAFF, B-cell activating factor of tumor necrosis factor family; BlyS, B lymphocyte stimulator; CAPS, cryopyrin-associated periodic syndrome; CD, Crohn’s disease; COPD, chronic obstructive pulmonary disease; CSS, Churg-Strauss syndrome; DM II, diabetes mellitus type II; FMF, familial Mediterranean fever; HES, hyper-eosinophilic syndromes; hlgG1, human immunoglobulin G1; IFN-α, interferon-alpha; IL, interleukin; IPF, idiopathic pulmonary fibrosis; LIGHT, lymphotoxin-related inducible ligand that competes for glycoprotein D binding to herpesvirus entry mediator on T cells; LT, lymphotoxin; Mab, monoclonal antibody; MS, multiple sclerosis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor-kappa B ligand; SLE, systemic lupus erythematosus; SolIA, systemic onset juvenile idiopathic arthritis; SSc, systemic scleroderma; TACI, transmembrane activator and CAML (calcium modulator and cyclophilin ligand) interactor; TGF-β3, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha.
Future directions

Recently, it was shown that MSU (monosodium urate monohydrate) and CPPD (calcium pyrophosphate dihydrate) crystals activate NALP3 inflammasome and that IL-1 plays a central role in driving acute inflammation during gout and pseudo-gout attacks [28]. In a small uncontrolled study and in case reports, anakinra has been proven to be very effective in controlling disease flares in patients with gout and pseudo-gout [29-31]. Rilonacet and canakinumab are under investigation in crystal-induced arthritides, and the preliminary results have been promising (Table 2 and [2]). In this context, targeting IL-1 could be a therapeutic alternative, at least for the cases of crystal-induced arthritis with refractoriness or intolerance to the standard treatment with nonsteroidal anti-inflammatory drugs, steroids, and colchicine.

The group of IL-1-mediated autoinflammatory diseases has been broadened with the addition of TNF receptor-associated periodic syndrome, familial Mediterranean fever, hyper-IgD syndrome, PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome, Schnitzler syndrome, systemic onset juvenile idiopathic arthritis, and adult-onset Still’s disease [11,16]. In the above inflammatory disorders, anakinra was remarkably effective [10] and, in the near future, it is expected that the novel IL-1-targeting therapeutics rilonacept and canakinumab will be useful treatment choices for these diseases.

Abbreviations

ASC, apoptosis-associated speck-like protein containing caspase-recruitment domain; CAPS, cryopyrin-associated periodic syndrome; CPPD, calcium pyrophosphate dehydrate; FCAS, familial cold autoinflammatory syndrome; FDA, US Food and Drug Administration; hlIgG1, human immunoglobulin G1; IL, interleukin; IL-1AcP, interleukin-1 accessory protein; MSU, monosodium urate monohydrate; MWS, Muckle-Wells syndrome; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne; RA, rheumatoid arthritis; SAA, serum amyloid A; TNF, tumor necrosis factor.

Competing interests

The authors declare that they have no competing interests.

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