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Perspective

Small-molecule inhibitors for autoimmune arthritis: Success, failure and the future

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ABSTRACT

Treatment of patients with aggressive autoimmune arthritis, such as rheumatoid arthritis (RA), is a considerable challenge for physicians, particularly rheumatologists. Because of the nature of autoimmune arthritis, effective and complete suppression of disease activity has been the primary therapeutic goal. Although currently available disease-modifying antirheumatic drugs (DMARDs) can successfully control the disease progression in a large proportion of patients, the benefit/risk ratio is not very much satisfied. The introduction of biologic agents such as anti-tumor necrosis factor-α, anti-interleukin-6, and anti-CD20 brings significant help to those patients with an inadequate response to treatment with DMARDs. In considering the limitation of currently available DMARDs and biologics, the development of new DMARDs, small-molecule inhibitors (SMIs), has recently emerged. In the past few years, a great volume of knowledge has been revealed from the experience of examining the usefulness of several SMIs for therapeutics of autoimmune arthritis. This paper addresses the up-to-date knowledge regarding autoimmune arthritis, therapeutics, findings from recently developed SMIs and the benefits and drawbacks of the development of SMIs. In addition, perspectives on the future development of SMIs for autoimmune arthritis will be described and discussed.

1. Introduction

Autoimmune diseases are a group of illnesses characterized by self-destructive processes that lead to systemic organ damages. Joint involvement (arthritis) is a common presentation for nearly all autoimmune disorders (hereby autoimmune arthritis), particularly so in the case of rheumatoid arthritis (RA), ankylosing spondylitis and psoriatic arthritis with joints as the primary target. Activation of immune effector cells such as macrophages, and T and B lymphocytes in autoimmune arthritis increases production of pro-inflammatory cytokines, chemokines, matrix metalloproteinases and many other proteinases that circulate in the bloodstream and accumulate in inflamed joints and cause joint destruction (Cooles and Isaacs, 2011). All these factors must be considered as a whole in developing therapies for autoimmune arthritis; otherwise, the therapeutic effect may be limited.

2. Current therapeutic strategies for autoimmune arthritis

2.1. Cyclooxygenase inhibitor

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a major group of fundamental drugs used to attenuate various inflammation-associated pain, like arthritis. NSAIDs inhibit prostaglandin synthesis through blocking cyclooxygenase (COX) activity (Vane, 1971). The bifunctional prostaglandin endoperoxide synthase isozyme (PGHS)-1 (COX-1) and PGHS-2 (COX-2) pathway is one of the major pathways of arachidonic acid metabolism leading to inflammatory reaction. COX-3 is a splice-variant of COX-1 with unclear roles in inflammation due to lack of COX activity in rodents and humans (Kis et al., 2005). It is generally accepted that the major adverse effects of NSAIDs such as gastrointestinal injury and renal function impairment are due to inhibition of COX-1, whereas the anti-inflammatory properties of NSAIDs are mainly from inhibition of COX-2. The COX-2-selective NSAIDs such as celecoxib, meloxicam and etoricoxib that preserve inhibitory selectivity on COX-2 have similar potency in pain-relief but less gastrointestinal and renal adverse events compared to those of conventional non-selective NSAIDs (Lee et al., 2005).

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2.2. Disease-modifying antirheumatic drugs

Current therapeutic strategies for autoimmune arthritis like RA utilize a combination of different immunomodulatory agents called disease-modifying antirheumatic drugs (DMARDs) (O'Dell, 2013). The most commonly prescribed DMARDs for autoimmune arthritis are methotrexate (MTX), hydrooxychloroquine, sulfasalazine, azathioprine, cyclosporin and leflunomide. Because these DMARDs preserve different immunomodulatory effects and mechanisms in immune effector cells like T lymphocytes (Ho and Lai, 2004), a combination of these agents can achieve synergistic effects in prevention of disease progression and joint deformity as well as in preservation of functional capacity of the joints (Fleischmann, 2013; O'Dell et al., 2013).

2.3. Biologic agents

Biologic agents, including those that target tumor necrosis factor (TNF, such as infliximab, adalimumab, certolizumab and golimumab), interleukin (IL)-1 (anakinra) and IL-6 (tocilizumab), inhibit the CD28 co-stimulatory signal (abatacept) or delete B cells (rituximab) are very useful and effective therapeutic modalities for patients with inadequate response to DMARDs (Choy et al., 2013; Smolen et al., 2014). Although the advantages of biologic agents are numerous, many limitations remain for all these biologics, including inconvenient administration (intravenous or subcutaneous injection), high cost and increased rates of infection, especially of tuberculosis and hepatitis (Dixon et al., 2010; Modena et al., 2013). Scientists in Sweden evaluated the socio-economic impact of RA and concluded that there is a 32% increase in the total fixed cost of RA between 1990 and 2010, a period covering 10 years before and 10 years after introduction of biologic agents (Kalkan et al., 2014). The increase of economic burden after introduction of the biologic agents has been reported worldwide and, in general, the combination of DMARDs remains to be the most cost-effective option for RA treatment (Eriksson et al., 2014; Wu et al., 2012). Another drawback for the biologic agents is the induction of immunogenicity leading to generation of a high-affinity B cell-mediated humoral response directed against biologic agents that greatly reduces their therapeutic effects (van Schouwenburg et al., 2013).

3. Recently developed small molecule inhibitors (SMIs) for autoimmune arthritis: failure and success

SMIs are a new generation of DMARDs. Given that the molecular targets and immunomodulatory mechanisms of many DMARDs remain unclear, SMIs are designed to target molecules of specific signaling pathways and/or mechanisms in cell activation (O'Shea et al., 2013b). In addition to targeting extracellular molecules, SMIs can specifically target intracellular molecules such as kinases, phosphatases, adaptors, scaffold proteins, transcription factors, and nuclear proteins. By interfering with the function of these signaling molecules, SMIs can change cellular structure, suppress cell growth, cell–cell interactions, signal transduction, gene transcription and protein translation or induce cellular death (O'Shea et al., 2013a). Cross-species contamination is also greatly reduced in SMIs.

3.1. p38 inhibitor

By observing that pyridinyl-imidazole compounds can inhibit production of IL-1 and TNF from stimulated human monocytes, using radiolabeled and radio-photoaffinity-labeled chemical probes, Lee et al. identified p38 as the target of these compounds (Lee et al., 1994). A variety of inflammatory stimuli or conditions, including pro-inflammatory cytokines, physicochemical stress, shock and infection, can induce signals through p38 in immune effector cells and synovial fibroblasts (Hope et al., 2009; Lee and Young, 1996). In mammalian cells, there are four isoforms of p38, namely p38α, p38β, p38γ, and p38δ. Different from both γ and δ isoforms that are mainly localized in certain specific tissues, the α and β isoforms are ubiquitous (Ono and Han, 2000). The roles of p38 isoforms have been investigated by genetic approaches. Compared to the knockout of p38α that is embryonically lethal (Allen et al., 2000), animals with the deficiency of p38β, p38γ or p38δ are viable, fertile and healthy (Beardmore et al., 2005; Sabio et al., 2005). In addition, a knockout of the p38β gene does not affect lipopolysaccharide (LPS)-induced cytokine production and development of TNF-induced arthritis (Beardmore et al., 2005). The inducible deletion of p38α in adult human TNF-transgenic mice, which avoids the embryonic lethality, decreases severity of arthritis and protects against TNFα-induced bony destruction (Bohm et al., 2009). However, a specific deletion of p38α in macrophages inhibits LPS-induced TNFα but not IL-6 production and has no effect on LPS-induced NF-κB activation (Kang et al., 2008). Analysis on inflamed tissues from patients with RA showed that p38α and p38γ among p38 isoforms are the major p38 isoforms activated in joint inflammation (Korb et al., 2006). In addition, IL-1β can activate both p38α and p38γ isoforms in human OA chondrocytes (Rasheed et al., 2010). Interestingly, recent studies showed that compound deficiency of p38γ and p38δ significantly reduces collagen-induced arthritis and expression of pro-inflammatory cytokines such as IL-1, TNFα and IL-17; however, a deficiency of either p38γ or p38δ has only intermediate inhibitory effect (Criado et al., 2014). Evidently, the role of p38γ in joint inflammation needs to be further investigated.

Because accumulated studies suggest that p38α appears to be the most important molecule among p38 isoforms in inflammatory response, many potent p38α inhibitors preserving anti-inflammatory properties were developed and at least 22 of which were investigated in phase I/II clinical trials for many autoimmune diseases. However, none of them progressed to phase III trials because of limited clinical efficacy and potential adverse events such as liver toxicities, serious infections, gastrointestinal disorders, and central nervous system disorders (Damjanov et al., 2009; Goldstein et al., 2010; Hammaker and Firestein, 2010; Terajima et al., 2013). Although the use of p38 inhibitors proved disappointing in treatment of autoimmune arthritis, their applications in other diseases warrant evaluation (Buhler and Laufer, 2014).

The failure of many p38α inhibitors in clinical trials due to lack of therapeutic efficacy and unacceptable drug toxicities in RA patients is somewhat un-expected. Several reasons such as inadequate dosing exposure, the potential anti-inflammatory property of p38α, the reduced lipophilicity and CNS penetration in drug designs, the redundant upstream signaling networks resulting in escape from p38 regulation have been proposed (Hammaker and Firestein, 2010). In addition, similar to the example of the protein kinase C isoforms (Fan et al., 2014), either pro- or anti-inflammatory effects of p38 isoforms may be present depending on their expressions in certain specific tissues and the signals triggered to activate these kinases (Chakravarty et al., 2013). For example, myeloid p38α is required for inflammatory infiltration, epidermal hyperproliferation, and hyperkeratosis in mice with chronic sodium dodecyl sulfate-induced skin injury (Kim et al., 2008). In contrast, given that p38α signaling in keratinocytes drives UVB-induced epidermal injury, myeloid p38α reduces UVB-induced vascular hyperpermeability (Kim et al., 2008).

Nevertheless, the experience from p38α inhibitors and JAK inhibitors (discussed below) suggests a possibility that higher level of inhibition may extend therapeutic efficacy and not necessary

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