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REVIEW

Kinase inhibitors: A new tool for the treatment of rheumatoid arthritis

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Abstract Despite aggressive immunosuppression with biologics and traditional DMARDs, achieving disease remission remains an unmet goal for most rheumatoid arthritis (RA) patients. In this context, there is a demand for novel treatment strategies, with kinase inhibitors expected to enrich the existing therapeutic armamentarium. In RA some kinases participate in the generation of pathogenic signaling cascades. Pharmacologic inhibition of kinases that mediate pathogenic signal transduction heralds a new era for RA therapeutics. Oral inhibitors of JAKs, Syk, PI3Ks, MAPKs and Btk are under development or in clinical trials in patients with RA. In this review, we discuss the scientific rationale for the use of kinase inhibitors in RA and summarize the experience from clinical trials.

Contents

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1. Introduction

Rheumatoid arthritis (RA) affects about 0.5–1% of the general population and is characterized by functional disability, as well as increased morbidity and mortality, mainly due to accelerated atherosclerosis [1,2]. Scientific breakthroughs and technological advances have deepened our understanding of RA pathogenesis. Novel genetic associations have been identified by genome wide association studies (GWAS) and the introduction of biologics has revolutionized the treatment of RA patients [1,3]. Despite this progress, there are still critical challenges and unmet needs. Synovial inflammation in RA typically has a chronic and unremitting character [4]. The current paradigm for the management of RA requires long-term administration of aggressive immunosuppression, which induces sustained remission in less than 50% of patients [5]. Notably, even in patients fulfilling the criteria for clinical remission, joint destruction may continue with repair of bone erosions rarely occurring, suggesting residual sub-clinical inflammation [6]. Thus, the nonresolving character of synovial inflammation serves as an obstacle for scientists and clinicians alike. A challenge in the field is to identify and characterize novel key players at the cellular and molecular levels that mediate unremitting synovitis.

Advances in delineating intracellular signaling pathways downstream of cytokine/chemokine/growth factor receptors and immunoreceptors involved in RA pathogenesis have set the stage for novel therapeutic strategies [1]. Signal transduction starts with the ligation of cell surface receptors, which then transmit signals to the intracellular space. Protein kinases are enzymes that transfer the terminal phosphate of ATP to serine, threonine or tyrosine residues in protein substrates. Since reversible protein phosphorylation is an essential mode of regulation of many cellular signaling cascades, kinases represent attractive therapeutic targets for a range of diseases, including cancer and immune/inflammatory disorders [7]. The recent development of orally administered small molecules, termed kinase inhibitors, which target the catalytic activity of kinases within cells and block the downstream pathogenic signaling cascades, has opened a new era in the management of RA. Currently, inhibitors of the Janus family of kinases (JAKs) [8–29], spleen tyrosine kinase (Syk) [30–32], phosphoinositide 3-kinases (PI3Ks) [33], mitogen-activated protein kinases (MAPKs) [34], and Bruton's tyrosine kinase (Btk) [35–39] are under development or in clinical trials in patients with RA. A major milestone for the use of kinase inhibitors in RA was the recent approval of the JAK inhibitor tofacitinib. Here we discuss the scientific rationale for the use of kinase inhibitors in RA and highlight its therapeutic use thus far from clinical trials.

2. History and pharmacology of kinase inhibitors

Approximately 2% of eukaryotic genes encode for protein kinases. The ability of certain natural products to inhibit protein kinases was first demonstrated by studies in the mid-1980s. Staurosporine, a natural product originally isolated from the bacterium *Streptomyces staurosporeus*, was found to potently inhibit protein kinase C (PKC). This discovery demonstrated for the first time that low (nanomolar) concentrations of ATP-competitive molecules could out-compete the high intracellular concentration of ATP (1–5 mM), thereby effectively inhibiting a kinase [40]. However, additional studies revealed that staurosporine is a highly promiscuous inhibitor with more than 90% of kinases inhibited by this compound [41]. Since kinases share extensive similarity in their ATP-binding pockets, the obvious concern was whether selective kinase inhibition could be achievable. In fact, the subsequent development of a number of potent and highly selective kinase inhibitors indicated that selectivity by ATP-competitive kinase inhibitors can be achieved by exploiting small differences in amino acid sequences and by selecting for compounds that preferably bind or induce distinct conformations of the target kinase.

Kinase inhibitors, according to their mode of binding to their target kinase, can be broadly distinguished into four classes: ATP-competitive inhibitors that bind the active conformation of the kinase (Type I), ATP-competitive inhibitors that bind the inactive conformation of the kinase (Type II), allosteric kinase inhibitors that bind outside the ATP-binding site, and covalent kinase inhibitors that form an irreversible, covalent bond with residues within the active site of the target kinase [42]. The study of the biochemical and biological consequences of different modes of binding of small molecule compounds to a given target kinase is an intense area of investigation. For example, a recent study on JAK inhibitors indicates that type II inhibitors (i.e. drugs that bind the inactive conformation) may represent different therapeutic strategies for the treatment of JAK-dependent diseases, as compared to the first generation type I JAK inhibitors [43].

3. Kinase inhibitors in RA

3.1. The JAK inhibitor tofacitinib

The family of JAKs includes the kinases JAK1-3 and Tyk2, which are associated with specific cytokine receptor subunits. Upon receptor ligation by the corresponding cytokine, the associated JAKs become activated and phosphorylate tyrosine residues in the receptors' cytoplasmic domains, thus creating