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Small-molecule therapeutics in rheumatoid arthritis: Scientific rationale, efficacy and safety

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A B S T R A C T

Rheumatoid arthritis (RA) remains a formidable clinical challenge. This is despite remarkable recent advances in our understanding of pathogenesis and the introduction of a variety of novel agents, particularly biologic therapeutics that are potent inhibitors of extracellular immune pathways. Whereas the latter have brought substantial improvements in efficacy and thus outcomes, there remain significant numbers of non- or partial responders to current standard of care. The discovery of key intracellular pathways, particularly kinases that subserve the function of these pivotal cytokine and immune cell receptors implicated in RA pathogenesis, has facilitated the advent of a new phase of RA drug development. Thus, a range of kinase inhibitors has entered clinical trials and one agent has been licenced for use in some regions. Herein we summarise the chequered history of kinase inhibitor development in RA, describing successes and failures alike, and thereafter examine future trends in this exciting field.

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Introduction

The last decade has been an exciting time for rheumatologists. Introduction of a range of licenced agents for rheumatoid arthritis (RA) has transformed the therapeutic landscape. There are now five biologic cytokine inhibitors of tumour necrosis factor-α (TNFi), biologic inhibitors of interleukin 1 and 6 receptor (IL-1, -6R), a depleting antibody directed against CD20 (B cell compartment targeting) and a protein construct binding to CD80/CD86 that thereby blocks the co-stimulatory signal required for the activation of T cells [1]. Moreover, biosimilar biologic products are either already or will be shortly approved and thus the range of options grows. Implementation in daily practice has been rapid, pending various health economic environments. Initial concerns for toxicity via immune suppression and immunogenicity (particularly for chimeric protein administration) have been largely quenched via clinical experience and meticulous data collection in registries. Management recommendations have been revised and the prescription of biologics is now routine in rheumatology clinics per protocol and upon observation of sufficient disease progression, or prognostic concern. Although their efficacy is established and a significant proportion of patients respond to these therapies at least partially, there are several issues that rheumatologists face daily. Side effects most commonly related to susceptibility to infection (e.g. tuberculosis, fungi, opportunistic organisms, viral infections) and rare serious adverse events (e.g. progressive multifocal leukoencephalopathy, demyelination) require constant vigilance. Diminution of effect over time perhaps related to development of anti-antibodies is common. Compliance, the route of administration (self-administered sc. injections, iv infusions at hospitals or clinics), co-medication with methotrexate (MTX) because of licence issues, cost burden to the health-care system require consideration. A major question concerns what strategy to follow at the outset of disease – most accept the need to treat early and aggressively, towards a target – but with what? When should one introduce a biologic agent, in whom and after what therapeutic experience? Similarly, we face challenges in choice of agents after several therapeutic failures – the so-called resistant disease. In a disease like RA that is prevalent in approximately 0.8% of the population and causes a significant disease burden with a high associated morbidity and mortality of affected individuals [1], these various issues comprise significant ongoing unmet clinical need despite recent advances.

This becomes even more important as we start to understand and adopt the idea of RA as a syndrome consisting of different pathogenic subsets with distinct molecular mechanisms as drivers behind the inflammation rather than a definite disease entity [1,2]. This syndrome in turn drives articular and systemic comorbid disease that demands a life-time approach with a range of 'modes of action' of agents ideally chosen in a stratified manner and on a pathogenesis ('disease stage specific')-driven basis. Considered thus, we have much work to do to secure the next steps in RA control.

Recent pharmacological research in RA has rediscovered the intracellular possibilities for immune modulation rather than only the extracellular milieu. In essence, the notion is that intracellular signal pathways that are now very well defined to subserve extracellular receptor function may facilitate rather effective leucocyte modulation if appropriately targeted [3]. After several setbacks, which will be discussed later in this review, this approach led finally to the approval of tofacitinib, a pan-Janus kinase inhibitor (JAK) with a higher affinity for JAK1 and 3, by the Food and Drug Administration (FDA) in 2012 for patients with RA and an inadequate response to MTX [4]. Thus, a new phase of RA drug development has been launched.

The varied, complex interactions of intracellular signalling pathways enable cells to respond and adjust to any environmental signal in an agile and dynamic manner. Signal pathways in reality are not a 'simple' pathway from cell membrane to nucleus, but rather an integrated network with numerous checkpoints and options for pathway crosstalk, perhaps explaining why several attempts have failed in the past: the p38 mitogen-activated protein kinase (MAPK) inhibitors represent a prominent exemplar in RA [5]. That a functional hierarchy exists however does hold true to some extent and allows conceptual targeting strategies to be devised. Functional signal pathways can be usefully considered as follows. An extracellular ligand binds to its receptor on the cell membrane, driving different intracellular mechanisms often via the activation of kinases. Kinases transfer a phosphate group from adenosine triphosphate (ATP) directly to their substrate, which can be another kinase, a different protein or a lipid (Fig. 1). Downstream of kinase interactions, activation or silencing of transcription factors occurs affecting the expression of their respective target genes. Thereby, change in the cell