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Review article

Treatment of rheumatoid arthritis: Unraveling the conundrum

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ABSTRACT

Rheumatoid arthritis (RA) is a heterogeneous disease with a complex and yet not fully understood pathophysiology, where numerous different cell-types contribute to a destructive process of the joints. This complexity results into a considerable interpatient variability in clinical course and severity, which may additionally involve genetics and/or environmental factors. After three decades of focused efforts scientists have now achieved to apply in clinical practice, for patients with RA, the "treat to target" approach with initiation of aggressive therapy soon after diagnosis and escalation of the therapy in pursuit of clinical remission. In addition to the conventional synthetic disease modifying anti-rheumatic drugs, biologics have greatly improved the management of RA, demonstrating efficacy and safety in alleviating symptoms, inhibiting bone erosion, and preventing loss of function. Nonetheless, despite the plethora of therapeutic options and their combinations, unmet therapeutic needs in RA remain, as current therapies sometimes fail or produce only partial responses and/or develop unwanted side-effects. Unfortunately the mechanisms of 'nonresponse' remain unknown and most probable lie in the unrevealed heterogeneity of the RA pathophysiology.

In this review, through the effort of unraveling the complex pathophysiological pathways, we will depict drugs used throughout the years for the treatment of RA, the current and future biological therapies and their molecular or cellular targets and finally will suggest therapeutic algorithms for RA management. With multiple biologic options, there is still a need for strong predictive biomarkers to determine which drug is most likely to be effective, safe, and durable in a given individual. The fact that available biologics are not effective in all patients attests to the heterogeneity of RA, yet over the long term, as research and treatment become more aggressive, efficacy, toxicity, and costs must be balanced within the therapeutic equation to enhance the quality of life in patients with RA.

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1. Introduction

Rheumatoid arthritis (RA) is a common autoimmune disease that can progress to disability, systemic complications, early death, and socioeconomic costs [1]. The pathophysiology of RA involves numerous different cell-types, including macrophages, B-cells, T-cells, chondrocytes and osteoclasts and synovial cells, all of which contribute to a local articular destructive process. Genetic and environmental factors appear to play a significant role in activating the immune system and eventually producing aberrant and sustained inflammatory responses [1]. Indeed, environment–gene interactions promote a loss of tolerance to self-antigens that contain a citrulline residue generated by post-translational modification, leading to an anti-citrulline response by both T-cells and B-cells. T cells, B cells and the orchestrated interaction of pro-inflammatory cytokines play key roles in the pathophysiology of RA. Differentiation of naïve T cells into T helper (Th) 17 cells results in the production of interleukin (IL)-17, a potent cytokine that promotes synovitis. B cells promote the pathogenic process through antigen presentation and autoantibody and cytokine production. Joint damage begins at the synovial membrane, where the influx and/or local activation of mononuclear cells and the formation of new blood vessels cause synovitis. Pannus, the osteoclast-rich portion of the synovial membrane, destroys bone, whereas enzymes secreted by synoviocytes and chondrocytes degrade cartilage. Antigen-activated CD4+ T cells amplify the immune response by stimulating other mononuclear cells, synovial fibroblasts, chondrocytes and osteoclasts. The release of cytokines, especially tumor necrosis factor α (TNF-α), IL-6 and IL-1, causes synovial inflammation. In addition to their articular effects, pro-inflammatory cytokines promote the development of systemic effects, including production of acute-phase proteins, anaemia of chronic disease serositis, vasculitis, cardiovascular disease and osteoporosis and affect the hypothalamic–pituitary–adrenal axis [2].

The past three decades, the efforts of the scientific community have focused on targeting the different branches of this complex pathophysiologic process, in order to achieve what we now apply in clinical practice, for patients with RA, the “treat to target” approach [3]. The current treatment strategy is to initiate aggressive therapy soon after diagnosis and to escalate the therapy, guided by an assessment of disease activity, in pursuit of clinical remission. However, several unmet needs remain. Current conventional and biologic disease modifying therapies sometimes fail or produce only partial responses and/or develop unwanted side-effects [1]. Remission at the molecular level and the capacity to reestablish immunologic tolerance still remain elusive. Elucidation of the pathogenic mechanisms that initiate and perpetuate RA offers the promise of progress in each of these domains.

The journey for the members of the scientific community, involving pathogenesis, diagnosis and treatment, has been long, yet rewarding. By this review we will depict the pathogenesis of RA-as yet understood-, make a historical review of the drugs that have been used through the years, present the drug target-molecules and their corresponding therapeutic agents, and finally propose some therapeutic algorithms.

2. A historic viewpoint of rheumatoid arthritis treatment

Both the objectives and the results of treatment for RA have changed profoundly over the past 25 years, dictated largely by an enhanced understanding of the pathogenesis of the disease.

In 1890, Koch showed that gold cyanide inhibited the growth in vitro of tubercle bacilli, and gold compounds were subsequently used to treat the chronic infection tuberculosis [4]. Hypothesizing a chronic infectious etiology for RA, Forestier pioneered the use of gold salts in RA [5], and they were subsequently shown to be effective by controlled studies [6,7]. Despite years of investigation, we know rather less about how gold evokes its anti-rheumatic effect than we do for most other drugs used in RA. Gold interferes with lymphocyte and monocyte function in vitro but not in vivo and reduces levels of immune complexes and rheumatoid factor (RF). The standards of older trials, such as those originally showing the short- and long-term efficacy of gold salts, were not always up to the standards employed today. The methodology applied in conducting clinical trials in RA is continually subject to improvement [8]. Until the introduction to the rheumatology clinic of methotrexate (MTX), imtramuscular (IM) gold, effective in the short and long term, was considered the standard disease modifying anti-rheumatic drug (DMARD) with which all other drugs were to be compared [9]; its major limitation, however, is its toxicity. Adverse effects occur in approximately one third of patients treated with IM gold. Common are trivial reactions such as post-injection reactions, mucocutaneous reactions (dermatitis, stomatitis, pruritus), deposition of gold into the cornea or lens, and dysgeusia. Less commonly seen, but potentially serious, are nephrotic syndrome, cytopenias including marrow aplasia, interstitial lung disease, and peripheral neuropathies. Thus, although undoubtedly effective in some patients, approximately one third of patients treated with parenteral gold stop the drug because of side effects, another third achieve a good clinical and radiographic response, and in the rest no response or toxicity is seen. In the era of biologic DMARDs and with the plethora of therapeutic options for RA patients nowadays, many clinicians no longer recommend it.

D-penicillamine, used in RA since the first successful case in 1964, is a degradation product of the antibiotic penicillin and a copper chelator, leading to the dissociation of immune complexes. It controls RA inflammation possibly by suppressing T cell function. D-penicillamine has never been shown to have the radiographic efficacy of parenteral gold and has many side-effects (bone marrow suppression, dysgeusia, anorexia, vomiting and diarrhea), including a weird spectrum of autoimmune phenomena (nephropathy, hepatotoxicity, membranous glomerulonephritis, aplastic anemia, antibody-mediated myasthenia gravis, Lambert-Eaton myasthenic syndrome, drug-induced systemic lupus erythematosus, elastosis perforans serpiginosa, toxic myopathies). Interestingly, a subpopulation of anti-Ro(SSA) positive patients with RA who receive D-penicillamine are of higher risk for developing side-effects, including skin rashes, proteinuria, leukopenia and autoimmune phenomena such as myasthenia gravis [10–12]. Few prescribe it actively now, and many younger rheumatologists have never done so. There appear to be no advantages when D-penicillamine is used in combination with other drugs [13].