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Review Article

Discoveries of conventional synthetic disease modifying anti-rheumatic drugs – Serendipity or flawless reasoning?

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ABSTRACT

Most of the conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) for treating rheumatoid arthritis (RA) were discovered serendipitously. Of course, discoveries do require serendipity, but it is not simply a random process or chance event. It is a process in which an unexpected event is seized upon by a creative mind that chooses to pay attention to the event, and unravels its mystery followed by its careful application for the benefit of mankind. Rheumatology is replete with such brilliant minds helping patients to come out from a hopeless illness and move towards a quality life that is almost as good as normal. In this short review, historical perspective of some of the older and current csDMARDs-related discoveries is described.

1. Introduction

Most of the conventional synthetic disease modifying drugs (csDMARDs) for treating rheumatoid arthritis (RA) were discovered serendipitously. Unfortunately, as Myer has opined, the meaning of serendipity is widely misunderstood.[1] In popular language, the term serves as a synonym for almost any pleasant surprise. More correctly, however, it refers to searching for something and stumbling upon an unexpected discovery of even greater value. Of course, discoveries do require serendipity, but it is not simply a random process or chance event. It is a process in which an unexpected event is seized upon by a creative mind that chooses to pay attention to the event, unravel its mystery, followed by its careful application for the benefit of mankind. Rheumatology is replete with such brilliant minds helping patients to come out from a hopeless illness and move towards a quality life that is almost as good as normal. In this short review, historical perspective of some of the older and current csDMARDs-related discoveries is described.

2. Anti-malarials

It is difficult to discuss anti-malarials without telling the fascinating story of the discovery of quinine. However, with limitations of a short review article on the discoveries of conventional synthetic DMARDs, that is not possible. Suffice it would be to state that the discovery of quinine is probably the

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most serendipitous medical discovery of the 17th century and for that the reader is referred to some key references.[2–4] Its use in malaria marked the first successful use of a chemical compound to treat an infectious disease.[5]

The use of anti-malarials in rheumatology, more specifically in the treatment of RA, also came into being serendipitously. Many physicians in those days had noted that the drugs of quinine family, besides curing malaria and the associated fever and shivering, also had ameliorating effect on a variety of skin diseases.[6] One of the recognised skin diseases was lupus, and during the 19th century, these drugs became widely used for cutaneous lupus.[6] In 1895, Dr. Thomas Payne, a physician in St. Thomas' Hospital London, recognised that anti-malarials might have more general healing powers in lupus, for example healing joint pains and fatigue.[6] During World War II, British physicians observed that soldiers with RA and systemic lupus erythematosus (SLE) improved while taking mepacrine (same as quinacrine, trade name atabrine), a synthetic acridine derivative of quinine, related to mefloquine, for malaria.[7] Page in his widely quoted 1951 landmark paper reported that mepacrine not only improved lupus erythematosus, but also one of his patients who had rheumatoid-type arthritis of 2 years duration.[8] This discovery paved the way for a century of 'anti-malarial' use in the various forms of rheumatological diseases, mainly lupus and RA. However, mepacrine had severe adverse effects including the most bothersome yellow staining of the skin. By that time, the earlier discarded drug resochin, now with a new name chloroquine (renumbered SN-7618), underwent a clinical trial in USA in 1946, and in this third attempt, it was found to be much superior to the then popular drug mepacrine (quinacrine, atabrine).[9,10] Thus, eventually chloroquine was recognised as a powerful anti-malarial drug and used extensively all over the world till recently. Accordingly, rheumatologists also shifted to using chloroquine, and the first trial demonstrating DMARD activity of the drug in RA was reported in 1960.[11] However, due to worries regarding the retinal toxicity, especially among patients with chronic intake of CQ,[12] it was largely replaced by its analogue, hydroxychloroquine. The latter was demonstrated to have better tolerability even at higher dosages. Also, when compared to CQ, HCQ retinal toxicity was infrequent.[13] This led to its trials in RA demonstrating its efficacy as a DMARD.[14,15] Based on these studies, it has become part of the conventional synthetic DMARDs, recommended by ACR/EULAR for the treatment of RA.[16,17]

Although this review is not intended to go in depth of the mechanism of action of the drugs discovered serendipitously, a summary of the mechanism of action of HCQ deserves mention. For details, the reader is referred to some recent reviews.[18–20] One of the key mechanisms of its action appears to be its antagonistic effect on Toll-like receptors (TLRs).[21] Several other mechanism of its action have been well-known for the last several decades, including interference with the antigen presentation, blocking UV light in cutaneous reactions and inhibiting phospholipase A2.[22,23] Specific mention needs to be made regarding the interference in the antigen processing and presentation that has been studied in depth.[24] Fox in 1993 reported that HCQ increases pH within intracellular vacuoles and alters the processes, such as protein degradation by acidic hydrolases in the lysosome, macromolecule assembly in the endosomes, and post-translational modification of proteins in the Golgi apparatus. Acidic cytoplasmic compartments are required for the protein antigens to be digested and for the peptides to assemble with the α and the β chains of MHC class II proteins. HCQ interferences with these steps result in diminished formation of peptide-MHC protein complexes required to stimulate CD4+ T cells resulting in down-regulation of the immune response against autoantigenic peptides that are now called damage-associated molecular patterns (DAMPs). In contrast, the pathogen-associated molecular patterns (PAMPs) that are not processed through this intracellular pathway are not interfered with. Thus, the immune system's protective role against pathogens is not interfered with. Thus the down-regulation of autoimmune reactions by HCQ seems to be rather specific without causing generalised immunosuppression. Based on recent reports of pivotal role of Th-17 subset of T cells and their cytokines in the pathogenesis of RA, a 2013 publication has also shown the effect of HCQ on Th-17 cells suppressing the production of its inflammatory cytokines. This and other effects of HCQ mentioned above could be underlying its immunomodulatory effect on proinflammatory cytokines (e.g. IL-1b and TNF-a, IL-6, IL-17 and IL-22.[25,26] Besides its immunomodulatory effect, HCQ has several additional beneficial effects, including glycaemic control in type II diabetes mellitus, controlling blood lipids and anti-thrombotic effect.[27–29] This has special importance for Indian patients. It is well known that the epidemic of metabolic syndrome is engulfing Indians rapidly.[30] Therefore, adding HCQ to other standard DMARDs (e.g. low-dose methotrexate) thus achieves dual purpose. On the one side, with its unique mode of action, it increases the efficacy of other csDMARDs (e.g. LD-MTX)[31]; on the other hand, it improves several parameters of metabolic syndrome as well.

3. Gold salts

The gold salts and D-penicillamine were popular and effective DMARDs in RA till about the late 1980s. The use of these drugs was however, based on faulty reasoning.[32] Way back in 1890, Robert Koch had discovered that gold cyanide was effective in vitro against *Mycobacterium tuberculosis*.[33] Based on this observation, Mollgaard in 1927 thought that gold salts have value in the treatment of tuberculosis.[34] Around the same time, some French workers in the field of arthritis had propounded the theory that RA was a manifestation of a certain form of tuberculosis in the joint.[35] The anti-inflammatory property of aurothioglucose had already been found beneficial for the management of articular symptoms in patients with rheumatic fever and endocarditis.[36] As in those days, RA was believed to be a manifestation of tuberculosis; the various gold salts began to be used for treating it and it was found beneficial in controlling the symptoms.[37,38] The first formal publication of its use in RA appeared in 1935[39] followed by the landmark paper by Cecil and colleagues in 1942.[37] Thus, gold salts became a standard drug for the management of severe RA until the 1980s when other DMARDs became popular for treating RA.