Treating Rheumatoid Arthritis Yesterday and Today

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Rheumatoid arthritis is a chronic, systemic inflammatory disorder that mainly affects joints. It is the most common form of inflammatory joint disease, and the second commonest joint disease, osteoarthritis being the commonest. The overall prevalence of rheumatoid arthritis has generally been given as 1% - with females outnumbering males in a ratio of 3-4:1, although there is some evidence that the incidence of the disease is decreasing.[1] Apart from this, the occurrence of rheumatoid arthritis is not the same throughout the world. It is quite rare in less developed rural parts of the world - thus one study in Nigeria failed to find one single case.[2] Studies in Europe have shown that there is a gradient in the prevalence of rheumatoid arthritis, starting from a low prevalence in the South (e.g. Italy 0.31%)[3] to a higher prevalence in the North (e.g. Finland 0.8%)[4] While no formal epidemiological studies on rheumatoid arthritis have been carried out in Malta, a total of approximately 600 patients with the disease are followed up at the Rheumatology Clinic at St. Luke's Hospital, giving a prevalence of 0.16%.

The first convincing description of rheumatoid arthritis is found in French medical literature in 1800.[5] However it is probable that the disease is much older than this.[6,7] The term rheumatoid arthritis was first used in 1859 by Sir Alfred Garrod, who distinguished the disease from gout. However, this term also included polyarticular osteoarthritis and, up until relatively recently, a number of seronegative arthritides, such as psoriatic arthritis. It was Sir Archibald Garrod, Sir Alfred's son, who distinguished rheumatoid arthritis from osteoarthritis in 1907. Aspirin was discovered by Bayer in 1899, and its anti-inflammatory properties were made use of extensively in the symptomatic relief of patients with various forms of arthritis, including rheumatoid arthritis. The development of phenylbutazone in 1949 ushered the era of non-steroidal anti-inflammatory drugs: these remained the mainstay of treatment of rheumatoid arthritis until the 1970s.

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By the late 1800s, which was about the time that rheumatoid arthritis had been described as a separate disease entity, the germ theory of disease had already been proven and accepted. Early studies on rheumatoid arthritis suggested that this disease might be a response to chronic focal infections; a specific strain of streptococcus as well as the tubercle bacillus were at various times considered to play a part in the etiology of the disease. It is therefore not surprising that the first attempts to treat the disease were directed towards removing infected foci from the body, such as tonsillectomies. Robert Koch's discovery that gold compounds could inhibit the growth of tubercle bacilli in vitro led to the introduction of gold salts in treating rheumatoid arthritis by Jacques Forestier in 1929.[8] Gold was eventually accepted as standard disease modifying treatment for rheumatoid arthritis particularly after the results of a major trial organized by the Empire Research Council were published in 1961.[9] In 1949 Forestier attended the 7th International Congress of Rheumatology in New York where he was to present his twenty year experience of treating rheumatoid arthritis with gold: however the key presentation of that meeting was one dealing with the effects of cortisone in chronic rheumatoid arthritis delivered by Philip Hench.[10] The effects of this medication were dramatic. A rapid improvement set in: pains and tenderness in the joints abated or disappeared and mobility increased, and for the first time since the onset of their disease patients who had previously been complete invalids could walk about freely, and their general condition was also favourably affected.[11] This discovery was considered to be so important that Hench and his colleagues were awarded the Nobel prize for Medicine in 1950. The corticosteroid miracle, however, was tempered by the serious side effects that started to appear after prolonged use of these medications, and for several years their use was not considered to be justified. Despite this, many rheumatologists continued to use steroids in some form or other to treat rheumatoid arthritis, and indeed there is currently renewed interest in their use.[12] An ingenious attempt to combine an anti-microbial and an anti-inflammatory agent resulted in the development of sulphasalazine by Dr. N. Svartz in the 1940s. However, a trial doubting its efficacy, as well as the arrival of cortisone, caused its use in rheumatoid arthritis to decline dramatically, only for it to be re-discovered about 30 years later.[13-15] Based on the possibility that rheumatoid arthritis may initially be triggered by an infection, there have been other

more recent trials where antibiotics have been used to treat rheumatoid arthritis. Thus, in 1999 a small study found that three to six months of minocycline therapy benefited early-stage rheumatoid arthritis patients for up to four years after treatment.[16]

Peruvian bark, which contains the anti-malarial agent quinine, was first used in treating fever and rheumatism in the 17th century. The first time that quinine was used successfully in the treatment of a rheumatic disease was in the late 1800s, when Payne, a physician to St. Thomas' Hospital in London, described its use in lupus erythematosus. In a paper by Page in 1951 it was reported that two lupus patients with associated arthritis had remission of their joint symptoms,[17] a finding that was subsequently confirmed by Bagnall.[18] Hydroxychloroquine was found to be equally effective and less toxic than chloroquine, and is today the anti-malarial that is most widely used in rheumatoid arthritis.

Penicillamine, a chelating agent that was first used by Walshe to treat Wilson's disease in 1955, was shown to dissociate macroglobulins such as immune complexes that contain rheumatoid factor. Studies in rheumatoid arthritis showed it to be effective in abut 60% of patients, but a high incidence of toxicity as well as lack of evidence that it prevents radiological progression have diminished its use quite considerably.[19,20]

Methotrexate was introduced as a disease modifying drug for rheumatoid arthritis in the late 1980s. This drug was originally introduced for the treatment of cancer, particularly childhood leukaemia, and it was first studied in low dose in arthritis in the 1960s. However, concerns surrounded the use of a chemotherapeutic agent in a chronic disease that at the time was not considered to have such a bad prognosis.[21,22] Renewed interest in the 1980s showed that doses as low as 7.5 mg per week could be beneficial in patients with rheumatoid arthritis. Several trials confirmed the efficacy and safety of methotrexate in rheumatoid arthritis in doses ranging from 7.5 to 20 mg per week, and it is now generally considered as the "gold standard" among the disease modifying drugs.[23-25]

Until the late 1970s the disease-modifying drugs available for the treatment of rheumatoid arthritis were considered to be either too toxic or relatively ineffective. At the same time, the prognosis of rheumatoid arthritis was generally considered to be fairly good, and that although the disease was incurable and painful, only rarely did it cause serious problems to patients,[26] with only 10% being severely disabled 10 years after discharge from hospital.[27] As a result the management of rheumatoid arthritis developed into a form of a treatment pyramid, starting with mainly symptomatic measures (such as physical methods of treatment and the prescription of non-steroidal anti-inflammatory drugs) with the use of disease-modifying drugs only being introduced when the disease progressed further.

Epidemiological studies from rheumatology centres over the past two decades have not confirmed that rheumatoid arthritis is such a benign disease.[28] Life expectancy is shortened by an average of about five years,[29] and a significant decline in functional status occurs over time, with about 50% of patients losing their jobs within 10 years of disease onset.[30] Besides, the long term outcome of traditional treatment of rheumatoid arthritis using the treatment pyramid, did not prove successful, with over 50% of patients having died or becoming severely disabled after 20 years.[31]

One of the more recent important discoveries in rheumatoid arthritis was that joint destruction, which is invariably preceded by synovitis, occurs early in the disease, and within three years of its onset, over two thirds of patients show radiographic damage, which is more pronounced during the first year of disease than during the second or third year.[32] These findings, together with the realization that disease-modifying treatments might be less toxic than was originally believed, and that the traditional treatment pyramid approach did not have any noticeable effect on the clinical, radiological progression and functional aspects and long term prognosis of the disease, had two important consequences on the treatment of rheumatoid arthritis. These were the reappraisal of treatment strategies, and intense ongoing research to develop new therapies that can delay or actually prevent joint destruction. The emphasis has now shifted to early diagnosis and treatment with effective disease modifying medication, either singly or in combination, to suppress inflammation as quickly and as completely as possible. Initial therapy may or may not include glucocorticoids.[33-38]

The other important consequence of the current approach to the treatment of rheumatoid arthritis has been a more intensive search to develop newer therapies with disease-modifying properties. One such medicine has been leflunomide. Unlike other medicines, with the possible exception of sulphasalazine, leflunomide was developed specifically for use in rheumatoid arthritis as well. The other disease-modifying agents used in rheumatoid arthritis had been in use for other indications before being found to be effective in rheumatoid arthritis. Leflunomide was discovered through an *in vivo* effect in the adjuvant arthritis rat model when it was shown to reduce the amount of paw oedema and to diminish the amount of skeletal decay.[39] Studies in humans showed the drug to be at least as effective as methotrexate; quality of life studies showed significant improvement with leflunomide over methotrexate. Compared with sulphasalazine, leflunomide showed superior physiological function, disease suppression and patient global assessment.[40-42] Careful monitoring of the drug is essential because of its potential heptatotoxicity. Furthermore, because of its long half life and teratogenic potential it has to be used very carefully in women of childbearing age.

The most exciting recent event in the field of rheumatoid arthritis treatment, however, has been the development of therapies targeted against specific mediators of the inflammatory cascade. At a cellular level, inflammation is a

process involving multiple cell types which produce various inflammatory cytokines that literally make the synovium a boiling pot of cytokines, chemokines and various other inflammatory mediators.[43] Of these, tumour necrosis factor alpha (TNF-α) and interleukin-1 (IL-1) have been identified as the major pro-inflammatory cytokines that, both directly and indirectly, lead to cartilage and joint damage that are the hallmark of rheumatoid arthritis. The isolation of the various cytokines has led to the development of drugs that target these cytokines, ushering in the era of biological treatment of rheumatoid arthritis. The most effective and widely used are the TNF-α inhibitors. This has been the first instance of a successful "bench to bedside" development which brought a targeted biological therapy for rheumatoid arthritis into clinical practice.[44] Three TNF-α inhibitors have been licensed since 1999: etanercept, a chimeric fusion protein where the tumour necrosis factor receptor is linked to the Fc portion of human immunoglobulin G, infliximab, a chimeric anti-TNF monoclonal antibody, consisting of mouse and human antibody, and adalimumab, a full human anti-TNF monoclonal antibody. The use of these drugs is associated with a high rate of rapid and substantial improvement in signs and symptoms in patients with rheumatoid arthritis, including those whose disease has proved resistant to conventional DMARD therapy. [45-47] The drugs may be used singly or in combination with methotrexate - combination therapy possibly being more effective showing sustained remission and, according to preliminary studies, reversal of joint damage.[48] Long-term safety data with these drugs is not available, but so far the main risk of side effects associated with the TNF-α inhibitors is that of infections, including tuberculosis. Studies of these agents in early rheumatoid arthritis are impressive, with a two year study of one of these agents (infliximab) combined with methotrexate seeming to inhibit the progression of structural damage and possibly even leading to healing of erosions: however, these results are still preliminary.[49] Due to the fact that TNF-α inhibitors are very expensive, as well as the concerns regarding their long-term safety, they are currently recommended for use in patients with rheumatoid arthritis who are refractory to other disease modifying drugs.[50]

The pace of development of treatments for rheumatoid arthritis has proceeded at a much more rapid rate over the past two decades than over the entire previous century. This rate of progress was possible because of the increased understanding of the pathogenesis of the disease leading to new strategies in controlling it. As a result, rheumatoid arthritis treatment has moved from the empirical use of agents such as gold to specific agents that target pro-inflammatory cytokines which are known to play a pivotal role in the pathophysiology of the disease. However, this is by no means the end of the story - the development of more potent immune modulators as well as newer approaches to switch off immune processes that are responsible for the development of the disease may result in even more effective therapy, promising an ever brighter future for patients with rheumatoid arthritis.

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