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Review Article

Rheumatoid arthritis: Treatment evolution over the years

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Introduction

Rheumatoid arthritis (RA) is a systemic, inflammatory autoimmune disorder affecting approximately 0.5-1% [1] of the general population. It is characterized by inflammation and proliferation of the synovial lining, leading to destructive changes within the synovial-lined joints [2], especially if left untreated. Patients suffering from RA, usually complain about pain and swelling of the affected joints as well as morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement [3]. As pain and stiffness are the cardinal symptoms, RA has a substantial impact on the quality of life (QoL) and patients should be regularly assessed and managed appropriately [4]. In addition, extra-articular manifestations are not infrequent. Among them, pericarditis, pleuritis, and cutaneous vasculitis are the most prevalent, but others such as neuropathy, scleritis, and glomerulonephritis may occur [5]. In order to better classify and manage earlier those patients, the 2010 Rheumatoid arthritis classification criteria have emerged [6] substituting the ones dating back to 1987 [7]. Since then, there is no doubt that in the field of rheumatology it has been achieved astonishing progress in the understanding and management of the rheumatic diseases including RA [8]. The progress has been achieved not only by the emergence of the newer drugs [9] but also the treatment strategies [10]. On the other hand, there are still unmet needs [11] despite all this progress and this subject is still a matter of debate [12] of what we are doing wrong in order to achieve complete remission in those patients [13].

The drug evolution in RA

Drug therapy has been evolved dramatically in the last 50 years. Rheumatologists used to treat their patients with

salicylates, non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids (cs), since the advent of the conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), biologic (b) DMARDs and lately the targeted-synthetic (ts) DMARDs.

The effectiveness of the salicylic acid in rheumatic disorders was first reported independently by two German physicians (Stricher and Reiss) in 1876, while in 1897, it had gained worldwide recognition in the treatment of pain [14]. However, the mechanism of action of NSAIDs remained elusive until the early 1960's when John Vane discovered it in 1971 increasing our ability to develop novel NSAID-therapies [15,16]. The real breakthrough in the treatment of RA has happened with the discovery of cortisone, a mysterious humour that improved RA with the name "substance X" [17]. In 1948, the first patient with RA received the "substance X" or later the "compound E" in the form of intramuscular injections of 50 mg, twice daily. On day 4, her pain and stiffness were gone and by day 7 she was able to go shopping. The so-called "substance X" or "compound E" later known as cortisone, led Philip Hench and Edward Kendall to receive the Nobel Prize in medicine and Physiology in 1950 [18]. Nowadays, the adverse reactions of NSAIDs and cs are well-known and should not be given for a long period of time [19,20]. Some years later, in 1962, Black et al, reported positive results with methotrexate (MTX) in RA and psoriatic arthritis (PsA) patients [21]. Since then, MTX is the most studied csDMARD with a safe and effective profile in the treatment of RA patients [22]. But, MTX alone does not typically results in drug-free remission and there is a significant proportion of patients that do not tolerate the side effects of the treatment. For the former, a combination of csDMARDs with or without cs has been tried [23] whereas for the latter switching to a different csDMARD was



the only solution [24]. The quest for better treatment options with less side effects and stronger therapeutic potency led to the discovery of the bDMARDs. In the late 1990s, the introduction of biologic targeted therapies [25,26] and in the last decade the development of the tsDMARDs [27] changed significantly the lives of RA patients. Biosimilars have also appeared after the expiration of the bio-originals' patent giving the opportunity to treat more patients by decreasing the treatment costs [28-30] Rituximab (RTX), a chimeric monoclonal antibody that targets the CD20 molecule expressed on the surface of B cells has been also approved for the treatment of RA patients that do not respond adequately to bDMARDs [31].

The evolution of treatment strategies in RA

Treatment strategies have also changed over those years. This evolution gone hand by hand with the discovery of new drugs. At the very beginning, the RA patient has been treated symptomatically using monotherapy regimens, bed rest and physical therapy. Later, and as the therapeutic options grew with the application of the csDMARDs more than one drugs had been employed (dual therapy and triple therapy – combination therapy) [32]. Then, other regimens have been tried such as the step-up therapy or aggressive schemes with high doses of cs and step-down afterwards with satisfactory results [33-35]. The main target of all these regimens was low disease activity or remission. Finally, in the era of the csDMARDs, bDMARDs and tsDMARDs more and more patients enjoy a life free of pain being in remission or in a low disease activity state In the future we may be able to personalise treatments in order to achieve even better results.

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