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Editorial

Rheumatoid Arthritis: Current Treatments and New Therapies

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Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects 1% of the general population. It is characterised by a dysregulation of the immune system that induces persistent synovitis and systemic inflammation, and can lead to joint destruction [1]. Despite a common clinical presentation, RA displays multiple pathogenic pathways.

The main aim of treatments in RA is to control inflammation and relieve symptoms, therefore preventing the joint damage. The current trend in practise is to treat the inflammation early so the disease can be controlled and facilitate remission [2]. This is in theory; in the practice however, not all RA patients respond adequately to treatments. Today, classic and novel treatments cooperate with targeted therapies and precision medicine to treat RA [3,4].

Non-steroidal anti-inflammatory drugs (NSAIDs), non-biologic and biologic disease-modifying anti-rheumatic drugs (DMARDs), immunosuppressants, and corticosteroids (GC) are some of the therapies used for RA. Methotrexate (MTX) as initial drug associated to short-term GC, has been until recently the gold standard for RA treatment, although now GC are recommended in association with DMARDs to maximise their effects [5].

Immune dysregulation in cytokines -especially TNFα and IL-6-, and key immune checkpoints have been used to develop new therapies for RA. The efficacy demonstrated in the prevention of bone erosions with early treatments -particularly anti-TNF therapy- supports the treat-to-target strategy [5].

New Therapies in RA

Monoclonal Antibodies

Antibodies directed at pro-inflammatory cytokines and T or B cell receptors are a line of treatment for RA patients, since activation of T and B cells is crucial in the immune response involved in the pathogenesis of RA [1]. Biomarkers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) provide information about disease activity, while rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) identify subjects susceptible to the disease and those with pre-clinical rheumatoid arthritis before the onset of symptoms [6]. Pro-inflammatory cytokines -Interferon (IFN) α and γ, macrophage inflammatory protein 1α (MIP1α), tumor necrosis factor α (TNFα), interleukin (IL)-37, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [7]-, as well as ACPAs and RF production released from B cells play a key role in the development of RA.

Some of these therapies with antibodies include anti-TNFα antibodies -infliximab, etanercept, adalimumab, golimumab and certolizumab pegol-; IL-6 inhibitors that block the signalling involved in pro-inflammatory mediating response -sirukumab and olokizumab-; anti-CD20 that deplete B cells -rituximab, ocrelizumab and ofatumumab-; or abatacept -a chimeric (cytotoxic T lymphocyte-associated protein 4-immunoglobulin fusion protein (CTLA-IgG)- with quite similar efficacy in RA respondent patients [8,9].

Blocking IL-17, IL-1, BAFF -B cell activating factor, also known as tumour necrosis factor ligand superfamily member 13B-, IL-21 and IL-20 appear to be a less effective treatment [10,11].

The inhibition of Th17 lymphocytes -a subpopulation of $CD4^+$ T lymphocytes that produces the pro-inflammatory cytokine IL-17 and seems to have a prominent role during the onset of RA– with secukinumab, ixekizumab and brodalumab is another avenue for treatments, and highlight the role of IL-17 in the pathogenesis of RA inflammation. In this regard, data available suggests a possible value of $CD24^{hi}CD27^+$ B cells and Th17 cells as predictor biomarkers of therapeutic response and may therefore guide the choice of tailored treatments [12].

FL-BsAb1/17 -a recombinant IgG-like bispecific antibody against IL-1β and IL-17A- also acts on anti-CCP antibody and down-regulate the expression of IL-1β, IL-17A, IL-6, TNF-α, matrix metalloproteinase 3 (MMP-3) and receptor activator of nuclear factor kappa-B ligand (RANKL), decreasing the IL-6 induced by IL-1β and/or IL-17A in fibroblast-like synoviocytes derived from RA patients [13].

Anti-JAK

Although recommended only after a biological DMARDs failure, the use of inhibitors of Janus Kinases (JAK) pathways –key in cytokines signalling via signal transducers and activators of transcription (STAT)- in early disease have recently showed substantial efficacy.

Still with some concerns for safety, tofacitinib -which inhibits JAK-1 and JAK-3- and baricitinib -which selectively and reversibly inhibits JAK-1 and JAK-2- are a new promising therapy for moderate-severe RA effective in inhibiting radiographic progression [10,11], while ABT-494 -a selective JAK-1 inhibitor- and VX-509 (decernotinib) -a selective JAK-3 inhibitor- are in phase of experimentation at the moment.

Mesenchymal Stromal and Stem Cells

Studies show that stromal mesenchymal stem cells (MSCs) regulate inflammation via immune response -through inhibition of T and B cell proliferation, suppression of natural killer and dendritic cell maturation, and promotion of anti-inflammatory macrophages [14].

Continuous research for treatments suitable to unresponsive RA patients -about 30% of patients- have led to promising results that show the ability of MSCs to restore immune system activity and repair the RA damage. Currently, there are several clinical trials on phase I and II in RA patients using this therapy.

Nanoparticles

The effect of treatments is limited by the bioavailability and the high dose necessary to overcome the clearance of the drug, which can induce side effects and unjustified iatrogenic damage. One of the ways to overcome this effect would be to deliver the therapeutic agent via Nano carriers or small liposomes to selective inflamed tissues and cells [15]. This promising novel therapeutic approach is currently being developed.

In summary, new target therapies that modify the course of RA have allowed a significant improvement in symptoms, radiographic progression and life expectation. However, more research into this area is still needed to discover pathophysiological mechanisms and factors involved in RA and ways to deal with symptoms and progression of the disease.

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