

**RHEUMATOID ARTHRITIS (RA)** is a chronic, progressive, debilitating auto-immune disease that occurs in approximately 1% of the population<sup>1</sup>. Although may develop at any age, RA occurs most commonly in people aged 40 to 70 years. Approximately 2.5 times more women than men are affected<sup>1</sup>. The disease is characterized by chronic inflammation of the synovium, which over time results in damage to the joints, leading to pain and disability<sup>2</sup>. The etiology of RA is unknown. Clinical and laboratory observations suggest an immune-mediated attack against self-antigens. This is demonstrated by the connection with the HLA-DR loci, and the presence of auto-antibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA)<sup>3</sup>. The immune-mediated background of RA is further underscored by the ameliorative role of immunosuppressive therapies. Once symptoms are present, RA manifests as a heterogeneous disease with a clinical spectrum ranging from mild to severe disease, and variability in secondary organ involvement. The heterogeneity of RA is most likely due to its multi-factorial nature, whereby specific combinations of environmental factors and a varying polygenic background are likely to influence not only susceptibility to the disease but also to its severity and prognosis. Unfortunately, the understanding of the preclinical phase and molecular complexity of RA is still incomplete and criteria for subtyping of patients, for example to select those who will benefit from a specific treatment, are currently lacking.

## TREATMENT OF RHEUMATOID ARTHRITIS

Disease heterogeneity is further illustrated by the current variation in treatment response rates. First-line treatment is usually initiated with so called traditional disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate (MTX). Approximately 30% of patients display a suboptimal response or intolerance to traditional DMARDs<sup>4</sup>. In these patients, second-line treatment is initiated with “biologics”, agents that block molecules or cells thought to be instrumental to disease progression, such as tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), interleukin-1 (IL-1) and B or T-cells. There are indeed nine biologic agents currently available, each with overlapping or unique mechanisms of action<sup>5</sup>. It has been observed that the response rates to such treatments vary widely, with a great number of patients remaining refractory to treatment or demonstrating only partial improvement.<sup>6 7 8</sup>

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<sup>2</sup> Choy, E.H. & Panayi, G.S. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N. Engl. J. Med* 344, 907-916 (2001).

<sup>3</sup> Rantapaa-Dahlqvist, S. et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum* 48, 2741-2749 (2003)

<sup>4</sup> Kooloos, W.M., Huizinga, T.W.J., Guchelaar, H. & Wessels, J.A.M. Pharmacogenetics in treatment of rheumatoid arthritis. *Curr. Pharm. Des* 16, 164-175 (2010).

<sup>5</sup> Isaacs, J.D. Antibody engineering to develop new antirheumatic therapies. *Arthritis Res. Ther* 11, 225 (2009)

<sup>6</sup> Hetland, M.L. et al. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. *Arthritis Rheum* 62, 22-32 (2010).

<sup>7</sup> Cohen, S.B. et al. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. *Ann. Rheum. Dis* 63, 1062-1068 (2004).

<sup>8</sup> Sibilila, J. Novel concepts and treatments for autoimmune disease: ten focal points. *Joint Bone Spine* 71, 511-517 (2004).