RHEUMATOLOGY ADVANCES IN PRACTICE

Rheumatology Advances in Practice 2017;0:1–2
doi: 10.1093/rap/rkx008

EDITORIAL

Editorial

Rheumatoid arthritis: the journey in pursuit of a cure

Since the dawn of documented presentations, RA has been a disease of great controversy. However, while the debate during the 18th and 19th centuries was on identifying RA as a distinct disease, it is now one on appropriate treatment and disease subtypes. Interestingly, from Alfred Garrod's first definition of RA in 1859, to arguably the hitherto most prosperous era in rheumatology at which we now stand, complete remission of the disease is rarely the norm [1]. In this commentary, I journey back in time to the ground-breaking discovery of anti-TNF as a therapeutic target, discuss the present armamentarium of drugs available against rheumatism and offer a perspective on the future direction of RA management and nascent paradigms.

RA is a systemic inflammatory disease with characteristics of autoimmunity. It is estimated to affect ∼1% of the population worldwide, with a distinguishable predilection for females, at a ratio of approximately 3:1. Important modifiable risk factors include obesity and smoking, whereas age, ethnicity and genetics also increase propensity to disease [2]. Interestingly, evidence points towards a protective effect of alcohol, the mechanism of which remains elusive. Ultimately, support for the involvement of the microbiome in the development of RA is increasing; *Porphyromonas gingivalis*, associated with periodontitis, as well as *Prevotella copri*, resident in the human gut, are the two primary suspects.

The pathophysiology of the disease is complex and not entirely understood. We accept that RA involves both the innate and adaptive branches of the immune system. Oddly enough, contrary to infection, the order of recruitment of effector cells is reversed; adaptive immunity precedes (and propels) the innate immunity in RA. Aberrant, self-reactive T cells from individuals with genetic susceptibility, combined with other risk factors in one's lifestyle, can suffice to trigger pathology. Subsequent to unusual T-cell activity, the innate branch of the immune system is eventually recruited and is responsible for most of the tissue damage that manifests symptomatically. Single amino acid modifications in protein residues can create neoantigens, against which the immune response is directed [3]. Citrulline is the main such amino acid against which antibodies are produced. However, the plethora of antibodies involved in RA does not demystify its pathophysiology. More specifically, RF and antibodies to citrullinated protein antigens are two widely recognized antibodies associated with RA. Surprisingly, the presence of disease in patients who are seronegative for both is not uncommon and lends support to the degree of variability in responses between different patients. Therefore, one might argue that RA is in fact a spectrum of various diseases, rather than one homogeneous entity. The significance of this debate is reflected when searching for a cure. Could there be a silver bullet against RA? Or is there a pending need for individualized therapy in patients? Certainly, in the endless pursuit for answers, we must not forget to strive to increase accessibility of current therapeutic modalities across patients. The motion (do not delay, connect today) derived from the 2017 EULAR annual conference reminds us all to make the effort to ensure that medications reach those in need. The platinum age for rheumatology, in which we find ourselves, should not be succeeded before resolving these fundamental principles [4].

The milestones in management of RA are several and recent. It was not until the late 20th century when Sir Marc Feldmann and Sir Ravinder Maini first identified the potential of TNF-α inhibition in the treatment of RA [5]. The results of the first clinical trial, in 1992 (Charing Cross Hospital, Imperial College, London), were only the beginning of a revolution in the field of rheumatism. To date, two drugs (infliximab and etanercept) capable of inhibiting TNF-α are ranked among the 10 largest selling pharmaceutical products. The third mAb with a similar mechanism of action (i.e. adalimumab) is currently ranked first in sales. Another triumph in the management of RA is MTX. Interestingly, despite all its pleiotropic effects, MTX also reduces the immune response to anti-TNF drugs, making it a widely applicable option for combined therapy in the arsenal against rheumatism.

Following the success of anti-TNF, a number of single-molecule inhibitors have been developed in an attempt to block activators of T lymphocytes. Anakinra against IL-1, tocilizumab against the IL-6 receptor and rituximab against CD20 are some noteworthy examples of currently available drugs. Last but certainly not least, abatacept acts by inhibiting co-stimulatory signals essential for T-lymphocyte activation. A clinical trial evaluating the efficacy of abatacept in the prevention of RA in high-risk populations is currently in its infancy. Another promising molecule is anti-CD28. Despite bearing great stigma after the lethal trials in Northwick Park under the name TGN1412, the latest studies have achieved inhibition of T-lymphocyte co-stimulation (as originally intended) with the molecule, sparing horrendous adverse effects (namely, the notorious cytokine

storm). The current panoply of anti-rheumatic drugs appears only to expand through the course of time. The question arising, however, is in what direction scientists need to delve to discover a definitive cure for RA.

Whilst still within the anti-TNF era, significant advancements on the horizon focus on different principles. One of the factors responsible for preventing anti-TNF treatments from fully abrogating arthritis is the response of patients to the treatment. Production of antibodies against exogenous anti-TNF can taper the therapeutic effects of these drugs. Although immunogenicity against anti-TNF dwindles at higher doses, administering the drug at such doses is not always preferable. Individuals differ from one another and mount unique responses with regard to the cytokines involved; in some patients, inflammation may be predominantly TNF-α mediated, whereas in others the expression of IL-1 or other cytokines at higher levels may comprise the paramount drive. In order to address variation among patients and the complexity of the cytokine milieu in their joints, another question demands investigation. Could patients with RA develop tolerance towards what they originally mount an immune response against? Progress in the field may reshape clinical practice, as Ranjeny Thomas and her group will proceed to run the first clinical trials of a vaccine for RA [6]. I therefore speculate an impending shift to a new era, with novel potential, by means of harnessing our own immune system. This is no other than the era of immune tolerance. Unequivocally, it would be an omission not to consider the role of the microbiome in disease. *Porphyromonas gingivalis* is capable of producing a similar enzyme to that responsible for citrullination in humans. The enzyme, peptidyl-arginine deiminase, may soon become a common drug target; unsurprisingly, there is a relevant clinical trial underway. Until the release of the findings, however, I remain hopeful that the answer for achieving remission in RA is hidden somewhere in the triad of anti-TNF, immune tolerance and microbiome regulation.

The beauty of RA is inherent in its complexity. Centuries of disease presentation paired with significant developments in research and treatment have shed light onto the pathophysiology of the disease, yet without a definitive cure in sight. Anti-TNF therapy, unarguably a revolution in the field of rheumatism, improves and will continue to improve quality of life in many patients with RA. With the current state of research, the promise of immune tolerance and the evidence for the involvement of the microbiome in disease may dramatically alter the way we view RA in the future. However, it is paramount to take into consideration that early or preventative interventions may come with side effects. These certainly need to be weighed, especially as the treatments will be administered to healthy individuals only at some risk of developing the disease. Additionally, such interventions are more likely to lead to illness behaviours, which further add to the challenge. Nevertheless, by acknowledging the aforementioned factors and evaluating the promising treatments on the horizon, we are one step closer to demystifying RA. Thereafter, the prospect of a definitive cure is what I hope shall follow.

Funding: No funding was received to aid in the production of this work.

Declaration of interest: The author of this work declares no competing interests.

Dimitrios Karponis[1,2]

[1]The Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, [2]Imperial College School of Medicine, Imperial College London, SW7 2AZ, UK
Accepted 4 October 2017
Correspondence to: Dimitrios Karponis, Flat 73 Alder Lodge, 73 Stevenage Road, Fulham, London SW6 6NR, UK. E-mail: dimitrios.karponis14@imperial.ac.uk

References

1 Garrod AB. *Treatise on the nature and treatment of gout and rheumatic gout*. London: Walton and Maberly, 1859.

2 Klareskog L, Catrina AI, Paget S. Rheumatoid arthritis. *Lancet* 2009;373:659–72.

3 Van Venrooij WJ, van Beers JBC, Pruijn GJM. Anti-CCP antibodies: the past, the present and the future. *Nat Rev Rheumatol* 2011;7:391–8.

4 The Lancet (Editorial). A platinum age for rheumatology. *Lancet* 2017;389:2263.

5 Feldmann M, Brennan FM, Maini RN. Role of cytokines in rheumatoid arthritis. *Annu Rev Immunol* 1996;14:397–440.

6 Benham H, Nel HJ, Law SC et al. Citrullinated peptide dendritic cell immunotherapy in HLA risk genotype-positive rheumatoid arthritis patients. *Sci Transl Med* 2015;7:290ra87.