Developments in rheumatology

Alan MacDonald

Alan MacDonald trained in Medicine and Rheumatology in Glasgow, Aberdeen and Liverpool before working as a Consultant Rheumatologist in Aberdeen, providing clinical care in all aspects of rheumatic disease to the population of North East Scotland including the Northern Isles of Orkney and Shetland.

He has had an interest in new medicines policy and Health Technology Assessment, as a member of the Scottish Medicines Consortium (SMC) between 2007 and 2020, serving as SMC Chair from 2017-2020. After formal retirement in 2022, he remained active in clinical practice supporting the clinical service in NHS Highland and working in guideline development with SIGN and NICE.

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Bill Ledingham's observations on the changing role of the orthopaedic surgeon in the management of severe inflammatory arthritis speak to the remarkable changes that we have witnessed in recent decades. As a rheumatologist, working in clinical practice over a similar time frame, it is hard to overstate the significance of these changes. The 'biologics revolution' has not only significantly enhanced treatment options and outcomes for patients, but, like all disruptive technologies, it has also brought about profound changes in the overall delivery of care. In nearly all respects this has been to the benefit of patients, though inevitably challenges remain.

Ledingham's article is also correct in referencing older treatments such as the use of gold salts. Whilst from a 21st century perspective, this may seem somewhat exotic, it is important to recognise those pioneers of our specialty, such as Jacques Forestier, whose belief that RA could be amenable to pharmacological manipulation was by no means obvious 100 years ago. By documenting and publishing the outcomes of patients that he treated with these compounds, he gave scientific validity to the concept of anti-rheumatic therapy and whilst the limitations of such drugs in terms of toxicity and limited long term efficacy became all too apparent, it would be wrong to forget the role played by those >>

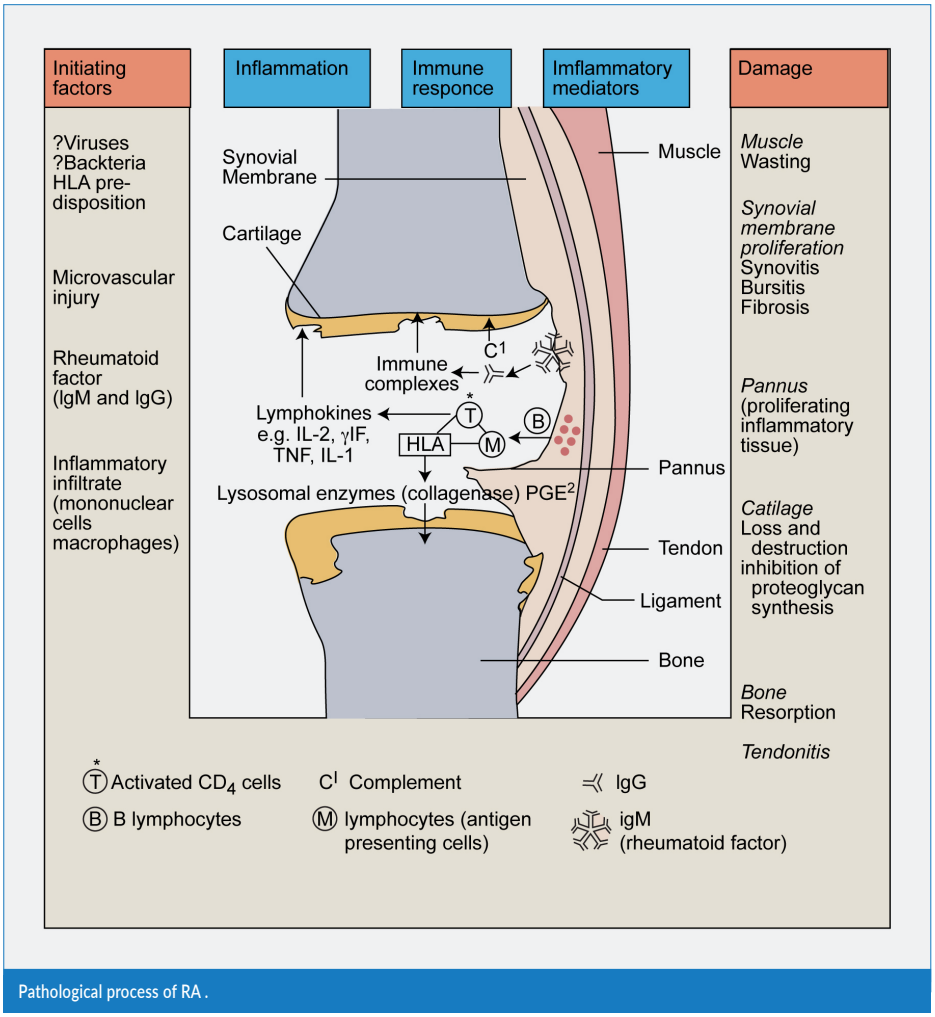
Typical forefoot and hindfoot deformities of rheumatoid arthritis. Hallux valgus deformity big toe with splaying of the forefoot and valgus deformity hindfoot.

whose work paved the way for rheumatology to become the dynamic modern specialty of my professional lifetime.

Before considering the impact of novel therapeutics, it is important to note the improvements in the use of conventional DMARD. Strategies such as earlier intervention, the use of drugs in combination and 'treat to target' strategies have all proven their worth. That methotrexate, offering benefits of high efficacy, acceptable toxicity and low cost, remains pivotal in management strategies speaks volumes to the importance of utilising all the available tools at our disposal.

Pivotal though methotrexate remains, the major paradigm shift has been the move from drugs with non-specific and often poorly understood effects on the disease process to medications targeted at key steps in these inflammatory cascades. Kickstarting this revolution was the study of the pro-inflammatory cytokine, tumour necrosis factor alpha (TNFa). Inhibition of this molecule was initially proposed as a potential target for treatment of sepsis but it was in the area of inflammatory disease that the fruits of these scientific endeavours were realised. The first commercially available TNFa inhibitors, Infliximab and Etanercept, were approved for use in the UK in early 2002.

Fast forward to the present and we have a bewildering array of options for the rheumatoid patient including five TNFa inhibitors, drugs directed against other pro inflammatory cytokines such as IL-6, monoclonal antibodies against B lymphocytes and those modifying T cell function and, most recently oral kinase inhibitors which block intra cellular pathways. It is tempting to believe that we now have the tools to render RA toothless, but of even dramatic advances such as these don't come without their challenges, which include toxicity, cost, patient selection and systems organisation.



Pathological process of RA .

Indeed, perhaps the greatest challenge for the practicing rheumatologist is knowing which drug or class of drug is most suitable for the individual patient sitting in the consulting room. Who is going to need early, aggressive intervention and with which class of drugs and who will do well on more moderate therapy such as modest dose single agent methotrexate? We have reasonable, though imperfect indicators of prognosis which are useful, but lack proven biomarkers to direct therapy and help us find the right treatment first time. Instead, we remain reliant on considerations such as cost, familiarity and patient preference. Scientific enquiry continues apace to improve this situation but, at the time of writing, the sort of personalised approach that is increasingly the reality in cancer therapeutics for example remains elusive in rheumatology.

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In terms of toxicity, many of the original concerns have not been realised. The policy of registering patients commencing biologics on large national registries has provided a great deal of high quality, real world data addressing initial anxieties around malignancy for example. Some data has suggested the possibility of increased cardiovascular toxicity in elderly patients receiving the new oral kinase inhibitors, though this may be less of a concern with the newer agents in this class such as Upadacitinib and Filgotinib. And, in spite of the overall favourable data on toxicity, it must always be borne in mind that these are potent drugs and increased risk of infection must always be considered.

And, for better or worse, the question of cost and value for money has never been far from the mind of those responsible for rheumatology services. Those of us who were in clinical practice in the early days of biologics well recall difficult discussions over patient access and the challenges of introducing high cost medicines into a hitherto low cost specialty, even when cost effectiveness thresholds had been met by the standards of bodies such as NICE and Scottish Medicines Consortium. From around 2016, we have been able to access many of these medicines at substantially lower cost by embracing the use of 'biosimilars', near identical copies with documented clinical equivalence.

Whilst these lower costs are welcome, the complexity of the manufacturing process does limit the extent to which costs may fall. With the ever greater range of options, the growing number of clinical indications and the likelihood of patients remaining on biologics for many years, overall affordability still remains a concern.

What does all this mean for the orthopaedic surgeon whose skills will continue to be needed by our patients? It is still recommended practice that biologic agents be paused prior to major surgery. Detailed guidelines on safety are available from professional bodies such as British Society for Rheumatology (BSR) and these include detailed guidance of the management of the peri-operative period.[1] There is acknowledgement that the evidence that biologic therapies increase peri-operative infection risk is conflicting and the risk of disease flare from discontinuing these drugs should also be factored in. Advice for specific drugs takes into account the half-lives of these agents, such that the drug Etanercept can be continued up to two weeks before the timing of surgery. For drugs with longer half-lives such as Abatacept, adopting this approach might require stopping the drug significantly earlier which may be challenging. A useful 'rule of thumb' therefore is that it is reasonable to perform surgery one week after the latest dose would have been due. Where time permits and overall infection risk is a major concern, one might consider a longer delay. Equally, the optimum time for restarting after surgery is not well defined, but with good wound healing, absence of overt infection etc., typically this could be 2-4 weeks. Trials are being undertaken to establish whether it is necessary to stop biologics in the perioperative period but the advice below should be heeded at present.

But ultimately the additional risks of surgery are those inherent to the patient more than any specific concern relating to their anti-rheumatic therapy and these include age, obesity, co morbidities etc. If surgery is deemed to be urgently required, the prescription of these medicines should not bring about delays that may ultimately prove more harmful to the patient.

A special mention should be made of whether methotrexate (MTX) increases the risk of infection in RA patients and whether it should be withheld prior to surgery. Historically methotrexate had been thought to potentially increase infection risk. However, recent evidence suggests that methotrexate does not significantly increase the risk of infection and not need not be routinely withheld prior to surgery.

A 2016 systematic review by Galvao *et al*. concluded that methotrexate did not significantly increase the risk of infection in RA patients compared to biologic therapies or other DMARDs[2]. The review suggested that withholding it might lead to disease flare and poorer surgical outcome with these outweighing the minimal increased infection risk associated with the drug. ■

References

1. Holroyd CR, Seth R, Bukhari M, Malaviya A, Holmes C, Curtis E, *et al*. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis-Executive summary. *Rheumatology* (Oxford). 2019;58(2):220-6.

2. Galvao TF, Zimmermann IR, da Mota LM, Silva MT, Pereira MG. Withdrawal of biologic agents in rheumatoid arthritis: a systematic review and meta-analysis. Clin Rheumatol. 2016 Jul;35(7):1659-68.

Drug	Dosing interval	Period in which surgery should be scheduled (relative to last biologic dose administered)	One half-life, days	Five half-lives, days
Adalimumab s.c	Every 2 weeks	Week 3	17	70
Abatacept i.v./s.c.	Monthly (i.v.) Weekly (s.c.)	Week 5 Week 2	14	70
Certolizumab	Every 2 weeks Every 4 weeks	Week 3 Week 5	14	70
Etanercept s.c	Weekly or twice weekly	Week 2	4	15
Golimumab	Every 4 weeks	Week 5	14	70
Infliximab	Every 6 - 8 weeks	Week 5, 7 or 9	9	45
Rituximab	Two doses 2 weeks apart, no more frequent than every 6 months	Months 4-7 Rituximab causes prolonged B-cell depletion, leading to impaired immune function with increased risk of infections	18	90
Tocilizumab I.V	Every 4 weeks	Week 5		
4mg/kg			11	55
8mg/kg			13	65
Tocilizumab s.c.	Every week	Week 3	13	65
Ustekinumab	Every 12 weeks	Week 13	21	105

Table 1: Dosing intervals, recommendations for timing of surgery and half-lives of biologic therapies. *Table adapted from Holroyd et al*[1].