IFSSH Scientific Committee on Arthritis
(Rheumatoid and other inflammatory conditions)

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What surgeons need to know about rheumatoid arthritis and its current medical treatment

Nothing has changed the face of rheumatoid arthritis (RA) as much as the medications that help to control the inflammatory aspects of the disease and reduce joint and soft tissue destruction in most patients. Because biologics not only act locally but also have a significant impact on the patient's immune system, they affect both the surgical treatment itself and patient management before, during, and after surgery.

RA is best characterized as an immune-mediated inflammatory disease. It is the most common inflammatory arthritis and affects about one percent of the population. The disease seems to be initiated by a complex combination of genetic predisposition and unknown extrinsic factors. The main tissue involved in RA is the synovial membrane in joints and around tendons. In RA, the synovial membrane is hypertrophied in all its layers, is heavily infiltrated by inflammatory cells and shows angiogenesis. The hypertrophied synovium, also called pannus, erodes cartilage and bone to leave significant defects. The driving cytokines in this process are interleukin-1 (IL-1) and tumor necrosis factor alpha (TNFα). Bone destruction is mainly driven by macrophage-induced osteoclast activation. A major development in the identification and prognostic factors of RA was the detection of antibodies to cyclic citrullinated peptides (anti-CCP), which are part of the autoimmune reaction. The presence of anti-CCP is more than 98% specific for the diagnosis of RA and generally represents a more aggressive phenotype of the disease. Rheumatoid factors are less specific for RA and are also found in other chronic inflammatory diseases, such as hepatitis C and tuberculosis.

There are many different pathways leading to this disease and no single disease agent that explains the pathogenesis. Interleukins, T and B cells, and macrophages interact in a complex manner to initiate and sustain the inflammatory process. This probably explains the different success rates of the various pharmaceutical agents.

The goal in treating RA is to gain control over the inflammatory processes in the synovial membrane and prevent joint destruction. The common principles that guide management strategies and the choice of medication were derived from an increased understanding of the disease and from evidence provided by clinical trials and other studies. The anti-inflammatory potency of the different drugs can be defined in a therapeutic pyramid. The first stage of pharmacotherapy includes non-steroidal anti-inflammatory drugs (NSAIDs), which mainly act as prostaglandin synthesis blockers. The next level consists of glucocorticosteroids, and then come the disease-modifying anti-rheumatic drugs (DMARDs). Methotrexate (MTX) is the best-known and most popular DMARD. It acts as an antimetabolite in the form of a folic acid analogue. Its main effect in RA depends on the inhibition of T cells.

Biologics, at the next level in the RA medication pyramid, were developed in the late 1990s. Their name was given according to the way in which they are synthesized, as genetically engineered proteins derived from human genes. Among the biologics, TNFα inhibitors are the first-line treatment after DMARD failure. All the other biologics are

not usually considered unless the therapeutic effects of anti-TNFα are not sufficient. Several targets besides TNFα are used to combat the complex inflammatory process in RA. Medication includes IL-6 blocking agents. They are often combined with MTX but can also be used as mono-therapy in cases of intolerance or contraindications to MTX. The newest developments are the bio-similars. These drugs are based on the different action modes of existing biologics. Because the older generation of these drugs no longer provide protection, the bio-similars are copying the mode of action but the bio-genetical engineering is different and cheaper. The average cost of biologics is up to USD 2000 per month, compared with about USD 70 per month for MTX alone. In order to justify the high costs, prediction of the individual response to treatment has become a major clinical challenge in RA.

Ideally, the goal of all of these drugs is remission of the disease, which is defined as the absence of disease activity but with the possibility of return. The remission rate of all these biological substances is around 50%, compared with a remission rate of around 30% for MTX alone. The adverse effects observed in RA patients treated with biologics are another concern. Besides the general adverse reactions, surgeons are especially interested in the discussion about possible increases in surgical site infections when immunosuppressants are administered in RA. Classic adverse reactions to MTX and even more to biologics include infections with opportunistic pathogens such as atypical fungi and mycobacteria. An increased risk of malignancies including melanoma is also suspected. Because the incidence of these adverse reactions is still low, most studies lack sufficient statistical power to provide evidence of a strong correlation.

Although several studies and long-standing personal experience show that MTX, even in combination with corticosteroids, does not increase the risk of surgical site infections, there are major concerns about the use of biologics in a perioperative setting. Based on several studies and personal experience, there is an informal expert consensus that interruption of the biological therapy is advisable for major surgical interventions such as joint replacement surgery, especially of larger joints. There is some debate as to whether corticosteroids and/or MTX should be given in the perioperative phase in order to reduce the chances of disease flare-up.

Interruption of biologics prior to surgery should be managed according to the administration time of the medication. Usually one cycle is omitted prior to surgery. The medication is restarted after the delay of another cycle or once wound healing is assured. However there are no precise data on this management.

Clinical observations indicate that the course of disease in patients with RA has become milder during the past decade. Less severe symptoms, as well as the diminishing need for orthopedic interventions, are most likely the result of the more potent drugs described previously in this chapter. There is an ongoing debate whether the type and frequency of surgical intervention have changed significantly in RA patients in recent years. Because the hand is still the main treatment target in these patients, as the hand is affected in almost 90% of patients ten years after the onset of disease, it can be used as an index intervention. Several studies have indicated a decline in the number of orthopedic interventions in RA patients over the last two decades, especially the

numbers of hand and foot interventions have declined in the western world. However, there are reports of possible changes in that trend, particularly in Japan. There are various possible explanations for this phenomenon. One possible explanation is that the new medications improve the patients' quality of life, which in turn increases their level of participation in social activities and work. These highly motivated patients place greater demands on both the functionality and the appearance of their hands and feet, so tend to seek surgical assistance more often. The appearance of the hands, as well as the feet, has a high value in societies like the Japanese, and deformities can lead to social isolation. The aesthetic aspects of these interventions should therefore not be underestimated.

Not only the number of surgical interventions has changed since the introduction of the new medications, but also the type of procedure. Previously common procedures such as wrist fusion and metacarpophalangeal arthroplasties have become rare nowadays, whereas other surgical interventions, including wrist arthroplasties and PIP replacements, are now seen more often in RA patients. There are reports about differences in the clinical and radiographic appearance of patients treated successfully with biologics. The radiographs started to look more like those of people with osteoarthritis than those of patients with chronic inflammatory disease. On the one hand, this has changed the indications for certain interventions because good medication has the potential to improve surgical results in the long-term.

Summary:

- Owing to modern treatment regimens, the number of surgical procedures has declined in most countries; however, there is a trend towards recurrence of the disease after 4-5 years of anti-TNFα treatment, possibly because of antibody formation to the medications.
- The pattern of RA patients being treated surgically has changed: these patients now either have isolated residual synovial inflammatory processes or are non-responders with a more severe pattern of disease showing gross destruction.
- Methotrexate and corticosteroid medication can or even should be continued during surgical procedures.
- Whether anti-TNFα medication should be discontinued during surgical intervention is still open to debate, as no clear evidence of a higher risk of infection can be found in the literature. If infection should occur, however, its course might be more severe.
- If anti-TNFα medication is discontinued, the administration interval of the particular biologic must be taken into consideration, as there are substantial differences between products.
- There is a subset of patients with a disease pattern resembling degenerative arthritis with a mild inflammatory reaction; these patients can be treated according to the surgical principles for degenerative arthritis.