Elective surgery in rheumatic disease and immunosuppression: to pause or not

A need for evidence-based approach

Whether or not to stop immunosuppressive therapy in the perioperative setting is a challenge for any clinician. Exacerbation of the inflammatory process would normally require increased immunosuppression; however, in this situation, it may lead to wound infection, with local or systemic sepsis, and potentially even lethal consequences.

Unfortunately, no data are available from randomized, double-blind, controlled clinical trials about the management of immunosuppressive therapy in the perioperative setting, making evidence-based recommendations difficult to say the least. Very limited evidence exists to determine whether the risk of infectious complications under immunosuppressive therapy differs according to the type and localization of surgery. Moreover, use of immunosuppressive co-medication such as dose of glucocorticoid is not adequately addressed in most studies, making their interpretation even more difficult. Decisions, therefore, must be made on an individual basis.

In chronic inflammatory diseases, drugs of many types, from small molecules to biologics, with varying levels of potency and affecting the immune system at many different levels, are used. Susceptibility to infection may be determined by the specific immune mechanism targeted, as individual immune mechanisms may be important in defence against different pathogens. For instance, T-cell depleting therapies are associated with increased rates of viral and fungal infections [1]. The extent of immunosuppression also depends on the dosage given [2]. Furthermore, combining drugs and inhibiting multiple immune mechanisms simultaneously has the potential to achieve yet greater immunosuppression—as shown by unacceptably high rates of infection and neutropenia, when combination therapy with an IL-1 receptor antagonist and a TNFi is used in patients with RA [3].

However, these pharmacological and pharmacodynamic considerations must be balanced by the often forgotten observation that chronic inflammatory processes in their own right seem to reduce defence against infection. Individuals with chronic arthritis seem to have a higher risk of infectious arthritis [4]. This increased risk may depend on the severity [4] of the underlying disease and is estimated to be up to 10-fold greater than those without [5].

When considering immunosuppressive therapy in surgery, one must also consider the effects that drugs, such as glucocorticoids, may have on wound healing. These drugs, frequently used perioperatively, mediate strong inhibitory effects on cell proliferation that, in turn, may compromise wound healing [6, 7] and increase the risk of infection.

While the risk of wound infection and compromised wound healing during immunosuppressive therapy is increased, the likelihood of exacerbating underlying inflammatory disease increases when immunosuppressive therapy is reduced or stopped. If clinical deterioration and a parallel rise in inflammatory markers occur in the presence of reduced immunosuppressive therapy, the physician faces the difficult situation of determining whether this process is caused by infection or exacerbation of underlying disease. Making the correct decision here is especially difficult. Withholding antibiotic therapy while continuing immunosuppressive therapy may increase the risk of sepsis, yet reducing immunosuppressive therapy may cause the patient to have a severe flare of the underlying inflammatory disease. If inflammatory exacerbation does occur, there may be a need to increase immunosuppressive therapy, often with glucocorticoids—yet increasing immunosuppressive therapy with a fresh wound site and reduced mobility may lead to higher risks of local and systemic infectious complications, such as pneumonia. However, reducing immunosuppressive therapy may potentially hamper recovery, as the disease flares. Patients with RA and severely inflamed joints may struggle to perform the necessary physical exercises to aid recovery, compromising the outcome of surgery and increasing the risk of post-operative morbidity, such as deep vein thrombosis, lung embolism and pneumonia.

There are many difficulties in interpreting the literature on perioperative management during immunosuppressive therapy. Different surgical procedures confer different risks of perioperative infectious complications, and the risk of infection depends on the duration, location and type of surgery (such as in primary or revision arthroplasty). Furthermore, the definition of wound infection is not standard. With regard to consequences for the patient and overall economic considerations, it seems reasonable to distinguish between superficial, deep and prosthetic infections. An estimated rate of overall perioperative infections in orthopaedic surgery is estimated to lie between 2 and 4% [8]. However, the risk of deep wound infection may also depend on the type of surgery, BMI, sex, race and other comorbidities—yet comorbidity is not always appropriately documented.

Considering all these points, we believe that the ideal approach is to apply the least immunosuppression...
possible, yet use as much as necessary—a most difficult balancing act. Of course, for each drug, the literature may reveal conflicting data and apparently support a variety of strategies. Therefore, it is the responsibility of the physician to make a decision to their best of their ability, based on the individual situation of the patient, while paying attention to the crucial dialogue between surgeon, rheumatologist and, of course, the patient. The individual patient’s situation must be assessed on the basis of their health and disease status, the history of the disease, the urgency, necessity and nature of the planned surgery, infectious complications in the past, the degree of immunosuppression and comorbidity.

In our own practice, we aim to stop immunosuppressive drugs 4–5 half-lives before a planned operation or, in the case of LEF, perform a wash-out with cholestyramine—to avoid, as much as possible, the wound or prostheses infections that can ruin a patient’s life. However, we accept that this is pragmatic advice, based on our experience of infections and inflammatory exacerbations. It is important to have a high index of suspicion for infection in all patients with inflammatory diseases, whether immunosuppressive medication is continued or not, so relevant diagnostic and therapeutic procedures can be instituted as fast as possible.

One thing is certain: there is a pressing need to generate data to allow a more evidence-based approach to this most difficult of areas. Many countries maintain registries on aspects of rheumatic diseases. Therefore, it might be worth considering the possibility of bringing together people from these registries, with the aim to include questions about this issue into the existing registry questionnaires to obtain sound data.

Disclosure statement: The authors have declared no conflicts of interest.

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Accepted 28 January 2010

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