Editorial

Elective Orthopedic Surgery and Perioperative DMARD Management: Many Questions, Fewer Answers, and Some Opinions...

Sometimes academic medicine generates scientific evidence that is unequivocal, but more commonly, the quest for answers to important clinical questions resembles a struggle that goes back and forth before leaning in one direction. All too often, there is a direct proportional relationship between the number of trials addressing a single scientific question and the confusion that surrounds it.

One of these questions is asked every day by rheumatologists and orthopedic surgeons: "Does my patient benefit from discontinuation of immunosuppressive therapy around the time of elective surgery in order to prevent peri- and postoperative complications? Or does this only add unnecessary risk of inducing a flare in disease activity?"

Numerous trials have failed to deliver convincing and consistent answers to this question[1-10]: their conclusions are limited by methodological problems including lack of explicit exposure or outcome definition, selection bias, and no matching or adjustment for known risk factors like age, site, or type of surgery.

Whether you favor "hold methotrexate around orthopedic surgery" or "continue methotrexate," you will find trials that support[5,10] or reject your case[3,6].

Why is this question so important? Because orthopedic surgical procedures are common in patients with rheumatoid arthritis (RA) and consequences of postoperative joint infections are usually grave: infection of a joint prosthesis often requires removal of the infected hardware and prolonged intravenous antimicrobial therapy. It is associated with functional decline, has a mortality rate of 2.7%–18%, and the cost of each infection episode is estimated to be in excess of $50,000[11,12].

There is no defined standard of perioperative care for patients receiving immunosuppressive therapies, and perceptions about the postoperative infection risk vary widely among physicians.

The increased risk of serious infections in patients treated with anti-tumor necrosis factor (TNF) agents[13-15] has brought perioperative disease modifying antirheumatic drug (DMARD) management back into focus. In this issue of *The Journal*, den Broeder, *et al* investigate the effect of perioperative anti-TNF treatment and other potential risk factors on the incidence of postoperative surgical site infections[16]. This retrospective parallel cohort study evaluates 1219 patients with RA who underwent elective surgical procedures. Interestingly, perioperative continuation of anti-TNF agents did not show a statistically significant association with surgical site infections.

Does this trial mark the transition from the dark ages of perioperative DMARD management to a period of enlightenment? Patients in this trial who continued anti-TNF agents perioperatively had a 50% increase in surgical site infections (OR 1.5). The nonsignificant p value of 0.43 points out the high danger that this difference between groups is due to chance and not based on a true effect; but we do not know which of the 2 explanations for this difference is correct. The nonsignificant p value does not allow us to conclude that there is no increase in surgical site infections for patients who maintained anti-TNF therapy. In this context, the confidence interval of the risk estimate is revealing: it ranges from 0.43 to 5.2, which means that assuming a baseline risk of 4%, the findings do not exclude even a major increase up to 20% with anti-TNF treatment. More important, this result is inconsistent with recent findings by Giles, *et al*[1], who detected an increased risk of surgical site infections with perioperative anti-TNF treatment.

"Here now I stand, poor fool, and see I'm just as wise as formerly." The question of adequate perioperative DMARD management resembles Goethe's Faust in his scientific midlife crisis: trapped in a bibliosphere of information, but still unable to get to the bottom of things.

Why is it so difficult to find a conclusive answer? Because answers to a research question are extremely difficult to find in the setting of a rare event, in the presence of multiple confounders, heterogeneous standards of care, dif-

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ferences in exposure (different drugs in different doses), and varying definitions of "surgical site infection" and its detection.

Postoperative surgical site infections are relatively rare, with a cumulative incidence between 0.5% and 6%, depending on the type and site of procedure. Assuming a risk of 4% of a postoperative prosthesis infection within the first year, it would require about 600 patients per treatment group to clarify whether continuing immunosuppressive treatment at the time of surgery doubles this risk. If a trial were to be focused on patients with high-risk surgeries (revision arthroplasty plus elbow or ankle), this number could be lowered to about 300 to 400 patients per treatment group.

The primary analysis presented by den Broeder, *et al* is based on 6 surgical site infections in 104 patients who continued anti-TNF treatment versus 8 events in 92 patients who discontinued it prior to surgery. Considering these numbers, the wide confidence interval, which does not exclude even a relative risk of 5, is no surprise.

Multiple potential confounders have to be taken into account. Severity of RA, "inflammatory burden," extraarticular disease, comorbidities, duration of surgery, site of surgery, revision versus primary arthroplasty: all have been associated with infection risk in patients with RA[17,18]. An observational trial would have to adjust for all these factors (and would not be able to adjust for the unknown factors). This further inflates the number of patients needed to achieve reasonable power to address the study hypothesis.

Den Broeder, *et al* adjust for 3 potential confounders (prior surgical site infection, elbow surgery, and duration of surgery) when analyzing the association between perioperative continuation of anti-TNF therapy and postoperative infections. Why only 3? Because the low number of events limits the number of predictors that can be included in a multivariate analysis. Why these 3? Because the authors only included variables that were statistically significant predictors of infection risk in a univariate analysis.

It cannot be emphasized enough that this strategy does not result in adjustment but in a prediction model, which carries a high risk of residual confounding: a variable that showed a nonsignificant p value as a predictor in a univariate model can still cause important shifts of the dependent variable in a multivariate model.

Heterogeneity in site and type of surgeries can threaten the validity of a trial that addresses postoperative complications if not accounted for. Clear and uniform definition of the type of surgery appears mandatory.

Den Broeder, *et al* list the sites of surgery; however, it remains unclear which types of elective surgery are compared in the final analysis. Bursectomies, tendon repairs, arthrodeses, and total joint replacements are unlikely to share the same postoperative risk, and imbalances in the relative distribution of these procedures between groups could seriously threaten the validity of every comparative analysis.

"Allein die Dosis macht, dass ein Ding kein Gift ist." [The dosage alone determines that a thing isn't poison]: the problem referred to in this much-cited statement by German physician Paracelsus is often difficult to acknowledge in observational research. While 3 mg/kg infliximab may not be a significant risk factor for infectious complications, the risk could be very different with 10 mg/kg[13], and while combination with 10 mg of MTX may be harmless, 25 mg may not be so. Further, the 3 anti-TNF agents have distinct biologic and pharmacokinetic properties that influence residual TNF activity with standard doses[19]. Therefore drugs and dosing included in an analysis should be uniform. If different agents and doses are lumped together, a trial may fail to detect associations because the significant effects of higher-dose groups or a certain type of anti-TNF agent are diluted by lower-dose groups and less potent (in terms of residual serum TNF activity) compounds.

Finally, a uniform and unequivocal outcome definition is of utmost importance: not every swelling, reddening, or painful prosthetic joint is an infected joint. Den Broeder, *et al* use the Centers for Disease Control criteria for surgical site infections; however, these have not been validated for elective orthopedic procedures, especially joint arthroplasty. Of note, only 44% of "surgical site infections" were culture-positive.

In light of the obstacles every observational trial will face when investigated for the association of perioperative DMARD management and the risk of surgical site infections, the question arises if any study will ever define the perioperative standard of care for patients with RA, whether with additional case-control or cohort studies.

And yes, at this point an editorial usually asks for a well performed randomized controlled trial to address the question: so be it. But considering the high number of patients that would be needed to perform such a trial with sufficient power, this would be a very costly undertaking.

In the most ambitious trial addressing perioperative MTX management, Alarcon, *et al* initiated a randomized, placebo-controlled, multicenter trial. After 2 years only 30 patients of a projected number of 144 were enrolled and the study was terminated. Many potential investigators declined to participate because of their strong opinions that MTX does or does not contribute to postoperative complications. Although this tells us a lot about the psychology of rheumatologists and orthopedic surgeons, it also points out additional problems a trial with anti-TNF agents may have to face.

So what are we going to do until convincing evidence becomes available — if it does at all?

Since we do not have enough data to either favor or reject an association of continuation of perioperative anti-TNF therapy, we will have to generate a preliminary risk-benefit analysis based on indirect information we already have.

Randomized controlled trials suggest that the risk of serious infections is increased in patients treated with anti-TNF

agents[13-15,20]. Recently, a large observational trial based on the British Society for Rheumatology Biologics Register detected an increased risk of soft tissue and skin infections in anti-TNF treated patients[21]. If we assume a baseline risk of 4% for a serious surgical site infection and a relative risk of 2 with perioperative anti-TNF treatment, discontinuing anti-TNF treatment around the time of surgery would lead to an increase of disease activity in 13 patients in order to prevent one infection. Considering the morbidity of orthopedic surgical site infections (especially prosthesis infections) as compared to a transient surge in disease activity, withholding anti-TNF agents perioperatively appears to be the most reasonable and prudent approach in this situation of uncertainty.

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