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QUESTION 4: How should patients currently using disease-modifying antirheumatic drugs (DMARDs) be managed in the perioperative period?

RECOMMENDATION: Spine surgeons caring for patients with rheumatic diseases must be aware that there are specific issues involved in their perioperative management. The optimal strategy for managing DMARD medications during the perioperative period of spine surgery is unknown due to the lack of evidence and it is largely based on low-quality evidence and expert opinion. A rheumatologist should be involved in the medication management around the time of surgery.

1. For nonbiologic DMARDs such as methotrexate (MTX), leflunomide, hydroxychloroquine and/or sulfasalazine, continuation of the current dose throughout the perioperative period is recommended.
2. For biologic DMARDs such as etanercept, we recommend that physicians withhold the biologic medication and plan elective surgery at the end of the dosing cycle for that specific medication. As an example, patients taking a weekly dose should schedule the surgery in the second week after the first withheld dose. These agents should not be restarted until external wound healing is complete, which is typically around two weeks. Exception: In patients taking tofacitinib (twice daily dose), withholding of tofacitinib for at least one week prior to surgery is recommended.
3. For medications typically used for systemic lupus erthematosus (SLE) patients, such as mycophenolate mofetil, azathioprine, cyclosporine and tacrolimus, the decision to withhold medications prior to surgery should be made on an individual basis.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Nonbiologic DMARDs

Although a reasonable concern exists about the potential of nonbiologic DMARDs to increase the risk of infection by affecting the immune response [1,2], stopping DMARDs prior to surgery may result in a flare-up of disease activity, which may adversely affect rehabilitation. Therefore, we suggest that patients continue the current dose of nonbiologic DMARDS throughout the perioperative period, including methotrexate (MTX), leflunomide, hydroxychloroquine and/or sulfasalazine. In clinical practice, the nonbiologic DMARD dose is often missed for one day and up to three days while the patient is hospitalized. Several studies of rheumatoid arthritis (RA) patients undergoing elective orthopaedic surgery have found that continued use of MTX through the perioperative period is safe [3,4]. A systematic review including four studies with RA patients undergoing elective orthopaedic surgery evaluated the effects of continuing MTX versus stopping MTX in the perioperative period [5]. Continued MTX therapy was safe perioperatively and was associated with a reduced risk of flares. There was no evidence to suggest that stopping MTX preoperatively reduced the incidence of infection or improved wound healing. However, in all of the studies, the mean dose of MTX was less than 15 mg per week.

The limited data on the use of leflunomide during the perioperative period is conflicting [6,7]. In one study, there were significantly more wound complications in patients taking leflunomide at the time of elective orthopaedic surgery compared with patients on MTX [7].

There are also limited data suggesting it is safe to continue hydroxychloroquine and sulfasalazine in the perioperative period. In a retrospective study of 367 orthopaedic surgeries among 204 RA patients, two-thirds of whom were receiving nonbiologic DMARDs including hydroxychloroquine and sulfasalazine, there was no increased infection associated with nonbiologic DMARD use [8].

Biologic DMARDs

We recommend that surgeons withhold biologic medication and plan the elective surgery at the end of the dosing cycle for that specific medication. As an example, patients taking weekly etanercept should aim to schedule the surgery in the second week after the first withheld dose. Patients taking adalimumab in two-week intervals should plan the surgery in the third week after the first withheld dose. In a similar manner, patients on monthly intravenous abatacept should schedule the surgery in the fifth week after the first withheld dose. Patients taking rituximab should wait until month seven after the last dose to schedule the surgery, presumably when B cells have returned to the circulation. However, nonelective procedures should not be delayed in patients who have been recently treated.

There is relatively little evidence available regarding the optimal timing for use of biologic DMARDs in the perioperative period, and our recommendation is largely based on indirect evidence suggesting an increased risk of infection associated with their use [9–11]. Many [12–16], but not all [17,18] retrospective studies suggest that use of tumor necrosis factor (TNF) inhibitors do not increase the risk of postoperative infections or impair wound healing.

The infectious risks of abatacept are similar to those of TNF inhibitors and other biologic agents, but there are no trials that have examined abatacept's safety perioperatively [9,19]. A case series described eight uncomplicated surgeries in seven RA patients on abatacept [20]. Similarly, there is no direct evidence regarding the safety of the interleukin (IL)-1 receptor inhibitor anakinra in the perioperative period. Conclusions regarding perioperative safety are largely based on trials in nonoperative patients showing that the infection rate was similar to that in patients receiving placebo [21].

These agents should not be restarted until external wound healing is complete, which is typically around two weeks. There is no evidence regarding the optimal time to restart biologic DMARDs in the perioperative setting and this approach is based on standard precautions used for biologic agents that warn against use in patients with active infection, such as an open wound.

Antirheumatic Kinase Inhibitor

In patients taking tofacitinib, we (Fang et al.) withhold the medication for at least one week prior to surgery. Tofacitinib is an orally-administered Janus kinase (JAK) inhibitor that is used in the management of patients with moderately to severely active RA. Our recommendation is based on indirect evidence from systematic reviews and meta-analyses of tofacitinib in nonsurgical patients showing there is an increased risk of infection with tofacitinib compared with placebo. Although the half-life is thought to be short for tofacitinib, there is uncertainty regarding the duration of immunosuppression after the drug is held [22].

Other SLE-specific Medications

There is uncertainty regarding the optimal perioperative medication management in patients with SLE given the lack of data. More data are needed to help guide perioperative medication management in lupus patients, including information on hydroxychloroquine, MTX, mycophenolate mofetil, azathioprine, cyclosporine and tacrolimus. Given the clinical spectrum of SLE disease severity and organ involvement, the decision to withhold medications prior to surgery should be made on an individual basis. Thus, for patients with severe SLE and multi-organ involvement in which discontinuation of the medication may result in a disease flare, it is reasonable to continue the medications through the surgical period. This is based on indirect evidence from organ transplant patients that supports continuing anti-rejection therapy during the time of surgery [23,24].

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