Medical management of patients with inflammatory arthritis undergoing total hip arthroplasty and total knee arthroplasty

Ioana Creţu* **, Mihai Bojincă* **, Mihaela Milicescu* **, Teodora Ţerban* **, Bogdan Creţu* ****, Ruxandra Ionescu* ***

*“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
**Department of Internal Medicine and Rheumatology, “Dr. Ion Cantacuzino” Hospital, Bucharest, Romania
***Department of Internal Medicine and Rheumatology, ”Sf. Maria” Clinical Hospital, Bucharest, Romania
****Department of Orthopaedics and Traumatology, University Emergency Hospital, Bucharest, Romania

Correspondence to: Creţu Ioana, MD, PhD, “Carol Davila” University of Medicine and Pharmacy, Bucharest, 8 Eroii Sanitari Blvd., District 5, Code 050474, Bucharest, Romania, Mobile phone: +40731 326 712, E-mail: ghinia.ioana@gmail.com

Abstract
Total joint arthroplasty (TJA) including total hip arthroplasty (THA) and total knee arthroplasty (TKA) are performed for patients with primary osteoarthritis (OA). Also, there are patients who undergo TJA for management of inflammatory arthritis (IA), including patients with rheumatoid arthritis (RA), Spondyloarthritids (SPA) including ankylosing spondylitis (AS) and psoriatic arthritis (PSA) and systemic lupus erythematosus (SLE).
The purpose of this review was to evaluate the current knowledge about the risk of complications after TJA in patients with IA and perioperative management of antirheumatic drugs.
THA and TKA are orthopedic surgeries that help patients with arthritis restore function, mobility and reduce pain. Patients with inflammatory arthritis have systemic disorders that cause a high rate of complications associated with the surgery.
Patients with inflammatory arthritis have systemic disorders that cause a high rate of complications associated with the surgery.
Information about cardiovascular risk factors and other comorbidities is important to better control and reduce the risk of postoperative complications.
Abbreviations
TJA = total joint arthroplasty, THA = total hip arthroplasty, TKA = total knee arthroplasty, OA = osteoarthritis, SPA = spondyloarthritids, IA = inflammatory arthritis, RA = rheumatoid arthritis, AS = ankylosing spondylitis, PSA = psoriatic arthritis, SLE = systemic lupus erythematosus, DMARDs = Disease-modifying antirheumatic drugs, PJI = prosthetic joint infection, VTE = venous thromboembolism, HCQ = hydroxychloroquine, SSZ = sulfasalazine, TNF = tumor necrosis factor, GS = corticosteroids.
Keywords: total joint arthroplasty, total hip arthroplasty, osteoarthritis, spondyloarthritids
Introduction

Total joint arthroplasty (TJA) including total hip arthroplasty (THA) and total knee arthroplasty (TKA) are performed for patients with primary osteoarthritis (OA) [1]. Also, there are patients who undergo TJA for management of inflammatory arthritis (IA), including patients with rheumatoid arthritis (RA), Spondyloarthritis (SPA) including ankylosing spondylitis (AS) and psoriatic arthritis (PSA) and systemic lupus erythematosus (SLE) [2]. Lower extremity arthroplasty is a successful way to decrease pain and improve function and mobility for patients with inflammatory arthritis [3].

In the past decades, rates of arthroplasty for patients with SPA have risen by 50%, for patients with SLE by 100% and for patients with RA have remained stable [4,5]. Orthopedic surgery for inflammatory arthritis may not be equivalent to patients with osteoarthritis due to joint deformities, bone loss and immunomodulatory medication [2,6,7].

Patients with IA are at higher risk of developing medical or surgical complications after orthopedic surgery because they have a systemic disease [2,8]. As an example, myocardial infarction has been reported to be between 0,6% and 6,5% for this population [9,10]. Also, patients with IA are at higher risk of infection, mechanical complication and transfusion [2]. Surgical site infection is two to four times higher in patients with RA than those with OA [10].

Immunosuppressive medication taken by patients with IA determines difficulty of perioperative management [6]. There are different types of treatments for patients with rheumatic disease. Corticosteroids are used to reduce inflammation. Synthetic disease-modifying antirheumatic drugs (DMARDs) and biologic DMARDs are used to suppress the immune system [3,11,12].

Guideline for the Perioperative Management of Antirheumatic Medications in Patients with Rheumatic Disease Undergoing Elective Total Hip or Total Knee Arthroplasty in 2017 is the collaboration between the American College of Rheumatology and the American Association of Hip and Knee Surgeons [13].

The purpose of this review was to evaluate the current knowledge about the risk of complications after TJA in patients with IA and perioperative management of antirheumatic drugs.

Complications

Patients with IA have a higher risk of severe complications after TJA than patients with OA [1]. The complications are different depending on the type of IA. Some studies have shown that SLE has a higher risk of complications than other IA [2,14]. Of all IA, most of orthopedic issues occur in the case of juvenile RA [2,15].

Infections occur more frequently in patients with inflammatory arthritis. Prosthetic joint infection (PJI) is a major complication of orthopedic surgery [16,10]. There are studies that show that PJI occurs 1,6-8 times more frequently in patients with IA than in patients with OA [17,18]. Bacteria that spread into the surgical wound are most often from skin flora and less commonly hematogenous spread. PJI is most commonly caused by Staphylococcus epidermis and the most common pathogen in patients with RA is Staphylococcus aureus [17,19].

In patients with psoriasis, surgeons should avoid making the incision through or near the active psoriatic plaque [17,20].

Patients with RA, SPA and SLE are at
higher risk of venous thromboembolism (VTE) compared to general population \([4,24]\). There is an association between inflammation and thrombosis, that is why rheumatic disorders should be controlled before the surgery \([4,25]\).

**Perioperative management**

In 2017, the American College of Rheumatology and the American Association of Hip and Knee Surgeons developed a guideline for the perioperative management of antirheumatic drugs for patients with IA \([13]\).

Medication used to treat patients with IA suppresses the immune system and may cause delayed wound healing and infection \([3]\).

| DMARDs: CONTINUE these medications through surgery. | Dosing Interval | Continue/Withhold |
|---|---|---|
| Methotrexate | Weekly | Continue |
| Sulfasalazine | Once or twice daily | Continue |
| Hydroxychloroquine | Once or twice daily | Continue |
| Leflunomide (Arava) | Daily | Continue |
| Doxycycline | Daily | Continue |

**BILOGIC AGENTS: STOP these medications prior to surgery and schedule surgery at the end of the dosing cycle. RESUME medications at minimum 14 days after surgery in the absence of wound healing problems, surgical site infection, or systemic infection.**

| DMARDs: CONTINUE these medications through surgery. | Dosing Interval | Schedule Surgery (relative to last biologic agent dose administered) during |
|---|---|---|
| Adalimumab (Humira) | Weekly or every 2 weeks | Week 2 or 3 |
| Etanercept (Enbrel) | Weekly or twice weekly | Week 2 |
| Golimumab (Simponi) | Every 4 weeks (SQ) or every 8 weeks (IV) | Week 5, 7, or 9 |
| Infliximab (Remicade) | Every 4, 6, or 8 weeks | Week 5, 7, or 9 |
| Abatacept (Orencia) | Monthly (IV) or weekly (SQ) | Week 2 |
| Certolizumab (Cimzia) | Every 2 or 4 weeks | Week 3 or 5 |
| Rituximab (Rituxan) | 2 doses 2 weeks apart every 4-6 months | Month 7 |
| Tocilizumab (Actemra) | Every 4 weeks | Week 2 | Week 5 |
| Anakinra (Kineret) | Daily | Day 2 |
| Secukinumab (Cosentyx) | Every 4 weeks | Week 5 |
| Ustekinumab (Stelara) | Every 12 weeks | Week 13 |
| Belimumab (Benlysta) | Every 4 weeks | Week 5 |
| Tofacitinib (Xeljanz): STOP this medication 7 days prior to surgery. | Daily or twice daily | 7 days after last dose |

**SEVERE SLE-SPECIFIC MEDICATIONS: CONTINUE these medications in the perioperative period.**

| DMARDs: CONTINUE these medications through surgery. | Dosing Interval | Continue/Withhold |
|---|---|---|
| Mycophenolate mofetil | Twice daily | Continue |
| Azathioprine | Daily or twice daily | Continue |
| Cyclosporine | Twice daily | Continue |
| Tacrolimus | Twice daily (IV and PO) | Continue |

**NOT-SEVERE SLE: DISCONTINUE these medications 1 week prior to surgery.**

| DMARDs: CONTINUE these medications through surgery. | Dosing Interval | Continue/Withhold |
|---|---|---|
| Mycophenolate mofetil | Twice daily | Withhold |
| Azathioprine | Daily or twice daily | Withhold |
| Cyclosporine | Twice daily | Withhold |
| Tacrolimus | Twice daily (IV and PO) | Withhold |

Fig. 1 Medications included in the 2017 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients with Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty. Dosing intervals were obtained from prescribing information provided online by pharmaceutical companies. DMARDs = disease-modifying antirheumatic drugs; SQ = subcutaneous; IV = intravenous; SLE = systemic lupus erythematosus; PO = oral (Source: Susan M. Goodman, Bryan Springer, Gordon Guyatt, Matthew P. Abdel, Vinod Dasa, Michael George, Ora Gewurz-Singer, Jon T. Giles, Beverly Johnson, Steve Lee, Lisa A. Mandl, Michael A. Mont, Peter Sculco, Scott Sporer, Louis Stryker, Marat Turgunbaev, Barry Brause, Antonia F. Shen, Jeremy Gililand, 104
Disease-modifying antirheumatic drugs (DMARDs)

Methotrexate is a folic acid analogue. It is most commonly used in the case of patients with RA [11].

Leflunomide inhibits pyrimidine synthesis resulting in blockade of T-cell proliferation [3,28].

Non-immunosuppressive disease-modifying antirheumatic drugs (hydroxychloroquine, sulfasalazine) are a therapeutic option for patients who cannot tolerate MTX or is contraindicated. Hydroxychloroquine (HCQ) is an antimalarial agent that inhibits the synthesis of nucleic acids. Sulfasalazine (SSZ) mode of action is unclear [28].

Biologic agents targeting tumor necrosis factor (TNF) increase the risk of infection, including surgical site infection. There are five types of anti TNF molecules: etanercept, infliximab, adalimumab, golimumab, certolizumab [28].

Rituximab is anti-CD20 monoclonal antibody and was initially used as a treatment of B-cell malignancies [28].

Corticosteroids (GS) are used in rheumatic disease for the anti-inflammatory and immunosuppressant effect. The most commonly used oral glucocorticoids are prednisone and intravenous methylprednisolone is most frequently used. Benefits of GS include benefits in disease activity and functional status. Patients who undergo long-term glucocorticoids treatment and major surgery must receive a prophylactic stress dose of glucocorticosteroids. 100 mg hydrocortisone three times per day is recommended [3,28].

Discussion

THA and TKA are orthopedic surgeries that help patients with arthritis restore function, mobility and reduce pain. Patients with inflammatory arthritis have systemic disorders that cause a high rate of complications associated with the surgery [1,26].

IA has prevalent complications depending on the subtypes. Some studies showed that SLE has higher complication rates than RA. Studies that evaluated subtypes of IA showed that juvenile RA had the highest orthopaedic complication rates, patients with SLE had high mortality rate and patients with RA and AS had increased wound complications [12,26].

Surgeons must apprise patients with IA that the incidence of periprosthetic joint infection is higher. Antibiotic impregnated cement might be considered in these patients [1,27].

The therapy used to control inflammatory arthritis causes suppression of immune system and increases the risk of infection, cardiovascular events, and delayed wound healing. The challenge is to reach a balance between a good management of the rheumatic disease and a reduced risk of postoperative complication [3,29].

Total joint arthroplasty in patients with rheumatic diseases should be performed after a multidisciplinary team consensus regarding the medication adjustment, to reduce the overall complication rate [4].

Conclusion

Patients with inflammatory arthritis, including RA, SPA, and SLE who need TJA have a higher risk of developing complications compared to patients with OA. It is important to recognize the risk these patients are exposed to in order to appraise them. Patients undergoing biologic treatment should stop the medication before surgery and patients with DMARDs should continue the treatment considering that it does not influence the evolution of the wound. Information about cardiovascular risk factors and other comorbidities is important to better control and reduce the risk of
Conflict of Interest statements
Authors state no conflict of interest.

References

1. Cancienne JM, Werner BC, Browne JA. Complications of Primary Total Knee Arthroplasty Among Patients With Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, and Osteoarthritis. J Am Acad Orthop Surg. 2016; 24:567-574.
2. Richardson SS, Kahlenberg CA, Goodman SM et al. Inflammatory Arthritis Is a Risk Factor for Multiple Complications After Total Hip Arthroplasty: A population-Based Comparative Study of 68,348 Patients. The J of Arthroplasty. 2019; 34:1150-1154.
3. Goodman SM, Figge M. Lower Extremity Arthroplasty in Patients With Inflammatory Arthritis: Preoperative and Perioperative Management. J Am Acad Orthop Surg. 2013; 21:355-363.
4. Goodman SM, Bass AR. Perioperative medical management for patients with RA, SPA, and SLE undergoing total hip and total knee replacement a narrative review. BMC Rheumatology. 2018; 2:2.
5. Mertelsmann-Voss C, Lyman S, Pan TJ, Goodman S, Figge MP, Mandl LA. Arthroplasty rates are increased among US patients with systemic lupus erythematosus: 1991-2005. J Rheumatol. May 2014; 41(5):867–74.
6. Goodman SM, Figge MA. Arthroplasty in patients with established rheumatoid arthritis (RA): Mitigating risks and optimizing outcomes. Best Practice & Research Clinical Rheumatology. 2015; 29(6):585–593.
7. Goodman S, Ravi B, Hawker G. Outcomes in rheumatoid arthritis patients undergoing total joint arthroplasty. International Journal of Clinical Rheumatology. 2014; 9(6):585-593.
8. Weinblatt ME, Kremer JM, Bankhurst AD et al. A trial of etanercept, are combinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. New England Journal of Medicine. 1999 January 28; 340(4):253–259.
9. Bongartz T, Halligan CS, Osmon DR et al. Incidence and risk factors of prosthetic joint infection after total hip or knee replacement in patients with rheumatoid arthritis. Arthritis Rheum. 2008; 59(12):1713-1720.
10. Schnaser EA, Browne JA, Padgett DE et al. Perioperative Complications in Patients With Inflammatory Arthropathy Undergoing Total Hip Arthroplasty. 2016; 31:2286e90.
11. Yeganeh MH, Kheir MM, Shahi A et al. Rheumatoid Arthritis, Disease Modifying Agents and Periprosthetic Joint Infection: What Does A Joint Surgeon Need to Know?. The Journal of Arthroplasty. Jan 2016.
12. Zampeli E, Vlachoyiannopoulos PG, Tsionus AS. Treatment of rheumatoid arthritis: Unraveling the 335 conundrum. J Autoimmun. 2015; 65:1–18.
13. Goodman SM, Springer B, Guyatt G et al. 2017 American College of Rheumatology/ American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antiinflammatory Medication in Patients With Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty. American College of Rheumatology. 2017.
14. Ravi B, Croxford R, Hollands S, Paterson JM, Bogoche E, Kreder H et al. Increased risk of complications following total joint arthroplasty in patients with rheumatoid arthritis. Arthritis Rheumatol. 2014 Feb; 66(2):254–63.
15. Merayo-Chalico J, Gonzalez-Contreras M, Ortiz-Hernandez R, Alcocer-Varela J, Marcial D, Gomez-Martín D. Total hip arthroplasty outcomes: an 18-year experience in a single center: is systemic lupus erythematosus a potential risk factor for adverse outcomes? J Arthroplasty. 2017; 32:34.
16. Schrama JC, Espehaug B, Hallan G et al. Risk of Revision for Infection in Primary Total Hip and Knee Arthroplasty in Patients With Rheumatoid Arthritis Compared With Osteoarthritis: A Prospective, Population-Based Study on 108,786 Hip and Knee Joint Arthroplasties From the Norwegian Arthroplasty Register. Arthritis Care & Research. April 2010; 473-479.
17. Premkumar A, Morse K, Levack AE et al. Periprosthetic Joint Infection in Patients with Inflammatory Joint Disease: Prevention and Diagnosis. 2018; 20:68.
18. Wilson MG, Kelley K, Thornhill TS. Infection as a complication of total knee-replacement arthroplasty: risk factors and treatment in sixty-seven cases. J Bone Joint Surg Am. 1990; 72:878–83.
19. Schrama JC et al. Risk of revision for infection in primary total hip and knee arthroplasty in patients with rheumatoid arthritis compared with osteoarthritis: a prospective, population-based study on108,786 hip and knee joint arthroplasties from the Norwegian Arthroplasty Register. Arthritis Care Res. 2010; 62:473–9.
20. Busti AJ, Hooper JS, Amaya CJ, Kazi S. Effects of perioperative anti-inflammatory and immunomodulating therapy on surgical wound healing. Pharmacotherapy. 2005; 25:1566–91.
21. Maradit-Kremers H, Crowson CS, Nicola PJ et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum. Feb 2005; 52(2):402-11.
22. Genga EK, Nalawade A, Oyoo GO. Perioperative management of patients with psoriatic arthritis: case report and literature review. East Afr Orthop J. 2015; 9:35–40.
23. Tobin AM, Veale DJ, Fitzgerald O et al. Cardiovascular disease and risk factors in patients with psoriasis and psoriatiarthritis. J Rheumatol. 2010; 37(7):1386-1394.
24. Kim SC, Schneeweiß S, Liu J, Solomon DH. Risk of venous thromboembolism in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2013 Oct;
25. Habe K, Wada H, Matsumoto T, Ohishi K, Ikejiri M, Matsubara K et al. Presence of Antiphospholipid Antibodies as a Risk Factor for Thrombotic Events in Patients with Connective Tissue Diseases and Idiopathic Thrombocytopenic Purpura. Intern Med. 2016; 55(6):589–95.

26. Rand JA, Ilstrup DM. Survivorship analysis of total knee arthroplasty: Cumulative rates of survival of 9200 total knee arthroplasties. J Bone Joint Surg Am. 1991; 73(3):397-409.

27. Wang J, Zhu C, Cheng T et al. A systematic review and meta-analysis of antibiotic-impregnated bone cement use in primary total hip or knee arthroplasty. PLoS One. 2013; 8(12):e82745.

28. Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH. Rheumatology. Chapter 4: Principles of management, 6th ed., 2015, Philadelphia, Elsevier, 451-581.

29. Ravi B, Croxford R, Hollands S et al. Increased Risk of Complications Following Total Joint Arthroplasty in Patients With Rheumatoid Arthritis. Arthritis and Rheumatology. Feb 2014; 254-263.