SYSTEMATIC REVIEW

Preoperative Evaluation and Management of Patients Receiving Biologic Therapies

Zahra Rezaieyazdi, MD; Maryam Sahebari, MD; Mandana Khodashahi, MD

Research performed at Rheumatic Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

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Abstract

The preoperative care of patients undergoing orthopedic surgery and treated with biologic agents is of great significance. Perioperative use of biologic agents could lead to such complications as infection and delayed postoperative wound healing. This narrative review aimed to evaluate the current information on the use of biologic agents in patients undergoing orthopedic surgery, determine the rate of associated postoperative complications, and identify the appropriate time for the continuation or discontinuation of biologic therapy in these patients. It can be stated that all biologic agents increase the risk of infections depending on their half-lives. Biologic agents are suggested to be withheld for at least twice their half-lives before major surgeries. However, in case of minor operations, they can be continued given the low risk of infection and impaired wound healing in these cases.

Level of evidence: I

Keywords: B cell inhibitor, Biologic therapy, Preoperative care, T cell inhibitor, TNF-α inhibitor

Introduction

Biologic therapy includes the use of living organisms and their derived substances to treat various medical conditions, such as autoimmune diseases (e.g., rheumatoid arthritis, seronegative spondyloarthropathies, and inflammatory bowel disease) and different types of cancers (1). Biologic agents are produced by applying recombinant DNA technology, in which vaccines or bacteria are adopted to stimulate the immune system (2). Biologic therapies have higher beneficial effects, compared to the conventional methods, because these approaches target the molecules involved in disease pathogenesis. However, the use of biologic agents is associated with some serious complications.

Although the use of biologic therapy is beneficial in patients with autoimmune diseases, surgery is an inevitable part of the treatment process of these patients. Some studies showed that the use of biologic agents could bring about some complications in patients undergoing surgery. Thus, these patients should be carefully evaluated for cardiovascular, pulmonary, hepatic, and hematologic problems (1). The rate of orthopedic surgery is particularly high in patients with rheumatoid arthritis (RA). Therefore, preoperative management in these patients is highly critical (2).

About 25% of RA patients undergo surgery during the first 20 years of the disease. The risk of postoperative infections varies between 0.5% and 6.0% depending on the type of operation and the surgical site (3). The incidence of surgical site infection (SSI) is estimated as 2-15% in the patients undergoing elective orthopedic procedures. Considering the possible impact of drug therapy on the incidence of postoperative complications in the patients undergoing elective orthopedic procedures, the perioperative management of biologic agents should be performed with caution (4, 5). It has

Corresponding Author: Mandana Khodashahi, Rheumatic Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
Email: mkhodashahi53@gmail.com; khodashahimn@mums.ac.ir

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been suggested that perioperative biologic therapy could enhance postoperative infection rates because these agents suppress the immune system. On the other hand, interruption of this therapy can enhance the probability of RA flares (6).

The RA patients are administered immunosuppressive agents during the perioperative period (7), which may lead to high infection rates in these patients. Therefore, the risk of flare and its association with the probability of infection or delayed wound healing should be considered. With this background in mind, the present narrative study was conducted to evaluate the current state of understanding regarding the preoperative management and postoperative complications of biologic agents in patients undergoing orthopedic surgery. This study was also targeted toward the determination of the appropriate time to discontinue biologic therapy in these patients.

Materials and Methods

In this narrative review, the authors assessed the preoperative use of biologic agents and determination of the appropriate time interval between the last dose and surgery. The agents under investigation included anti-tumor necrosis factor alpha (anti-TNF-α, e.g., etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol), anti-T-lymphocytes (e.g., abatacept), and anti-B-lymphocytes (e.g., rituximab).

We included articles that assessed preoperative use of biologic agents in patients undergoing orthopedic surgeries. For the purpose of the study, the articles related to the subject of interest were searched in several databases, including PubMed, Scopus, Google Scholar, and Science Direct. The search process was accomplished using the following keywords: "Anti-TNF-α" or "TNF-α inhibitor", "Anti-T-lymphocytes" and "Anti-B-lymphocytes", "Abatacept", and "Rituximab" in combination with "Preoperative care" and/or "Preoperative services", and/or "Preoperative management".

All of the retrieved papers were clinical trials written in English language and published in the last 15 years (i.e., during 2002-2017). Two researchers, who meticulously evaluated the retrieved articles in terms of the inclusion and exclusion criteria, performed the search process. The number of the articles cited in each database was specified, and the duplicate articles were omitted.

The studies hat reported the effect of biologic agents (i.e., anti-TNF-α drugs, anti-T-lymphocytes, and anti-B-lymphocytes) on postoperative complications were included in the study. On the other hand, the articles that involved the use of non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief in patients with RA were excluded from the review process. Additionally, letters to the editor, opinion articles, review articles, meta-analyses, expert opinions, consensus statements, and qualitative studies were excluded.

We only reviewed the articles assessing RA and spondyloarthropathies including ankylosing spondylitis, reactive arthritis (including Reiter's syndrome), psoriatic arthritis, inflammatory bowel disease-associated spondyloarthropathy, and undifferentiated spondyloarthropathy. Studies on other rheumatic diseases were excluded from this study. The exclusion criteria were: 1) investigation of autoimmune diseases other than orthopedic disorders, 2) not investigating the effects of biologic agents on postoperative complications, 3) lack of sufficient data, and 4) poor description of the applied methods.

Search outcome

First, the abstracts of the articles were assessed and those meeting the inclusion criteria were included for further evaluation. The initial evaluation was performed on the abstracts and titles of the manuscripts. Then, the articles reporting the postoperative complications in the patients receiving biologic therapy were selected, and those failing to meet this criterion were excluded for the review process. The initial evaluation resulted in the identification of 95 clinical trials examining preoperative care in patients treated with biologic agents and subjected to orthopedic surgery. Out the 95 manuscripts, 65 cases were excluded due to the investigation of the effects of other biologic agents on postoperative complications (n=15), unavailability or insufficiency of the data (n=21), adoption of a review and meta-analysis design (n=26), and use of a qualitative design (n=18). Finally, the full texts of the selected articles were reviewed and data was extracted with respect to our objectives. After elimination of unrelated articles, 23 left for further assessment.

In the next stage, the selected articles were classified into three categories based on the type of the biologic agents. These groups included anti-TNF-α agents (n=15), anti-T-lymphocytes (n=1), and anti-B-lymphocytes (n=1). The extracted information included the type of biologic agent, sample size, major findings, and interval between the last dose of biologic therapy and surgery. The selection process is exhibited in the PRISMA flow diagram [Figure 1]. In this review, evidence was obtained from RCTs (randomized controlled trials; level I). Table 1 tabulates the summary of the collected data.

Results and Discussion

There is a scarcity of data on the postoperative complications of orthopedic procedures in patients receiving biologic therapy. Accordingly, the impact of specific biologic agents on the risk of postoperative complications, such as infection and wound healing, in patients with inflammatory rheumatic diseases remains inconspicuous. The high risk of infection in RA patients and the probability of developing other complications as a result of biologic therapy in this population highly challenge the decision-making process regarding the proper therapeutic regimen (8).

In the RA patients undergoing orthopedic surgery, the main risk factor for postoperative complications is the use of immunosuppressive agents. In these patients, a polysaccharide matrix resistant to the host defense mechanisms may be produced at the bone-prosthesis interface by a biofilm. This leads to bacterial growth, thereby increasing bacterial infection in RA patients

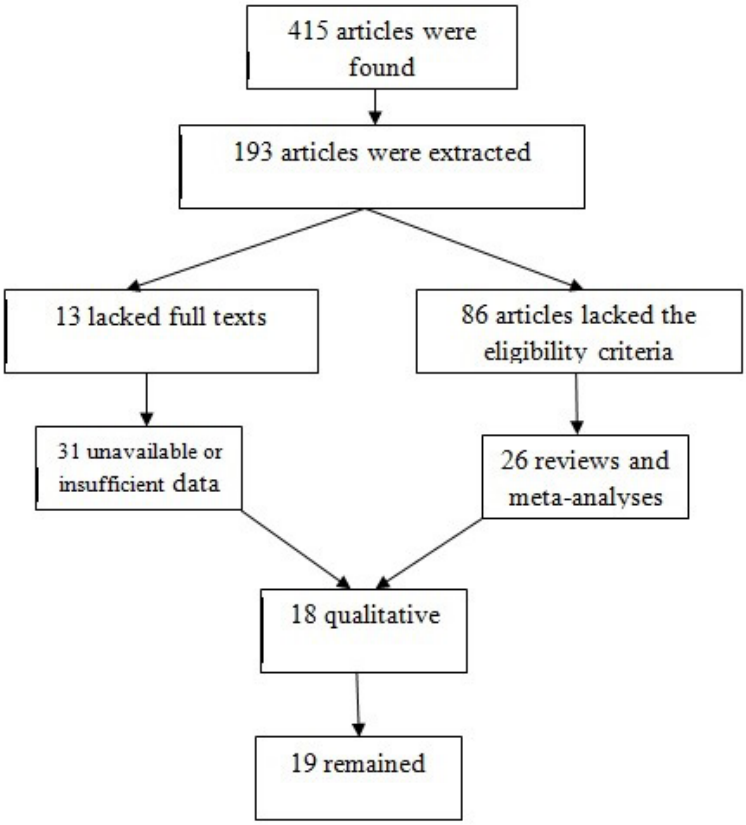

Figure 1. PRISMA flow diagram of the reviewed articles.

undergoing arthroplasty (9).

TNF-α inhibitors

Interruption of anti-TNF therapy before operation is a critical issue; however, there are limited data in this regard. Perioperative management is an issue of paramount importance in the patients with RA and other inflammatory rheumatic diseases under anti-TNF therapy. The consumption rate of anti-TNF agents in RA patients increased to 22% in 2004; moreover, the rate of surgery in these patients is on a growing trend (10). Although many studies have evaluated the side effects of anti-TNF therapy in RA patients, the rate of postoperative complications and the timing of treatment discontinuation have not been clearly determined yet.

The perioperative risk of TNF-α therapy has been assessed in many studies, some of which have shown that TNF blockers increase the probability of postoperative infections (10-14). Other studies have reported contradictory results in this regard (10, 15, 16). The TNF-α plays an important role in host defense against intracellular organisms; therefore, its neutralization and short interval between the last anti-TNF-α infusion and operation may elevate the probability of infection (17).

So far, 15 studies have assessed the perioperative safety of anti-TNF agents for orthopedic surgeries (6, 8-10, 12, 13, 15-24). There are contradictory results regarding the association between the applied TNF-α inhibitor and postoperative infections. Five studies reported that the rate of postoperative infections was higher in the patients who continued anti-TNF-α therapy (6, 9, 18-20). However, nine studies showed no association between anti-TNF-α therapy and postoperative infection (8, 10, 12, 13, 16, 17, 21-23). Furthermore, a number of the reviewed study indicated an association between anti-TNF-α therapy and other complications, such as septic arthritis, arthralgia, and deep venous thrombosis (DVT) (18, 23). Based on the results obtained by Bibbo et al., TNF-α inhibitors had a higher effect on the reduction of infection rate and improvement of wound healing than the other disease-modifying antirheumatic drugs (DMARDs) (15).

Based on a study performed by den Broeder et al., the interruption of TNF-α therapy does not affect the risk of surgical site infection (SSI) in RA patients. However, the incidence rates of wound dehiscence and bleeding were higher in patients who continued anti-TNF, compared to those in the patients interrupting TNF-α therapy. The most important risk factor for SSI is the history of SSI or skin infection, which may be caused by relative

Table 1. Summarized suggested times for discontinuation of the studied medications before surgeries

Agents		Complications	Optimal Dose	Time of preoperative discontinuation of medication	Time of postoperative consumption of medication
Anti-TNF alfa	Infliximab	Postoperative infections septic arthritis, arthralgia, deep venous thrombosis (DVT) wound dehiscence, bleeding surgical site infection (SSI) , flare-up of arthritis,Reactivation of latent TB	Optimal dosing is affected by disease severity and patients' condition. Usually between 3-5 mg/kg IV at weeks 0-2-6 then every 8 weeks	Commonly, infliximab is stopped less than one dose prior to surgery. Usually, 4 weeks due to half-life and type of surgery 16-19 days for two half-lives and 40-47 days to five half-lives	3-4 weeks after regardless of agent type and depending on the time of wound healing commonly 10-14 days after wound healing
	Etanercept		50 mg SQ weekly	Etanercept is discontinued about two doses prior to surgery. Commonly, 2-4 weeks depending on the type of surgery 7 days for two half-lives 14.5 days to five half-lives	12 days after regardless of agent type and depending on the time of wound healing commonly 10-14 days after wound healing
	Adalimumab		40mg SQ every other week	Adalimumab is discontinued about two doses prior to surgery. Comonly, one month before operation (14 to 56 days) 20-40 days for two half-lives 50-100 days to five half-lives	56 days
	Golimumab		50 mg SQ monthly	4 weeks , dependent on orthopedic surgery, patient's conditions, and drug dose regimen	Not clarify yet
B-cell inhibitor: Rituximab		Hypogammaglobulinemia ,which can lead to the development of infection, SSI delayed wound healing, skin fibrosis, Hepatitis B reactivation	Optimal dosing is affected by disease severity and patients' condition. 1000mg IV day0 and 14 repeat course every 24weeks	Mean interval between the last dose and operation is 6_+ 4 months, RTX treatment can remain for 2-3 weeks and last up to 12 months after treatment interruption	Not clarify yet
T-cell inhibitor: Abatacept		SSI and delayed wound healing	Optimal dosing is affected by disease severity and patients' condition. Usually it is infused <60Kg: 500 mg 60-100kg :750 mg >100Kg:1000mg At weeks 0,2,4 and then every 4 weeks or 125 mg SQ weekly	Nearly 16 days , 2-3 weeks to14-day half-life, 8 days and 3 weeks with a mean value of 13.1 days depending on patients' conditions.	5 weeks after the last preoperative infusion delayed for a week after wound healing (10-14 days).

immunodeficiency or Staphylococcus infection (10). These findings were confirmed by other similar studies (21).

Kubota et al. compared biologic therapy with non-biologic treatments and observed no significant differences in wound healing and infection in RA patients (22). In another study, it was demonstrated that the rate of surgical wound complications in the patients receiving TNF-α inhibitors was not different from that in the patients receiving DMARDs. In the mentioned study, the durations of wound healing and fever were statistically equal between the two groups (16).

In another study performed on the patients undergoing total hip and knee arthroplasties, superficial SSIs were reported in 5.7% of the patients, which resulted in the

removal of the artificial joint prosthesis in 0 .7% of the cases. The mentioned study also marked an association between infection and the use of biologic DMARDs. In addition, the risk of infection was raised as a result of administering TNF-α inhibitors, infliximab, and etanercept. Therefore, the use of TNF-α inhibitors was withheld before operation (19).

Kawakami et al. found arthralgia in less than one-third of the patients receiving etanercept. They showed that SSI and DVT were the two main postoperative complications due to anti-TNF therapy in RA patients (18). Thrombus formation is inhibited by TNF-α because it reduces platelet activation. Accordingly, the prevalence rate of DVT was higher in the patients receiving anti-TNF than that in DMARD group (25). In another study, it was shown that anti-TNF therapy in RA patients increased the risk of septic arthritis (23).

Talwalkar et al. observed no perioperative infections in the patients under anti-TNF-α therapy and those who discontinued treatment. They observed RA flare only in one patient who stopped etanercept treatment at the time of surgery (12). However, Wendling et al. showed that the rate of flare was higher in the patients who interrupted TNF-α therapy than that in the patients who continued this treatment (13).

There are limited data on the flare-up of arthritis during recovery from surgery, which is characterized by increased joint pain and swelling, and sometimes, fatigue and low physical activity (26). Therefore, the incidence of flare after surgery may put patients at high-risk situations, compromise surgical outcome, and impede the proper continuation of the therapeutic regimen (27).

Infection is considered the main side effect of anti-TNF-α treatment in patients with rheumatic diseases; however, a limited number of prospective studies have been conducted on this issue. Therefore, these drugs should be administered with caution in the perioperative period. In the reviewed articles, continued and interrupted anti-TNF therapies were performed based on different guidelines and considering the type of orthopedic surgery, patient's conditions, and drug dose regimen. Despite the concerns over the use of anti-TNF-α medications, the majority of studies indicated a low risk of postoperative infection in the patients receiving these medications (28-31).

The chemical half-lives of anti-TNFs do not necessarily determine the appropriate dosage of anti-TNF. In this regard, the biological effectiveness of the drugs and their bioavailability should be considered in determining the optimal dosing regimens (12). The findings on discontinuing anti-TNF therapy are inconclusive as they are affected by different factors, such as disease severity (32).

There are different clinical guidelines for the administration of TNF-α inhibitor (31, 33). Some of these guidelines are comprehensive and take into account the risk of infection, wound healing, and flare with treatment discontinuation (29). Some guidelines have addressed planning to stop treatment before surgery while failing to determine the appropriate time of treatment resumption (18).

Various national rheumatologic societies have proposed different guidelines for perioperative anti-TNF therapy. In general, the effects of anti-TNF agents disappear after a period of five half-lives (14). According to the guidelines put forth by the American College of Rheumatology, the use of biologic agents should be stopped at least one week before operation and restarted one week after surgery (28). However, the Canadian Rheumatology Association guidelines suggested to interrupt biologic agents two half-lives before surgery (34).

According to the British Society for Rheumatology, TNF therapy should be withheld 3-5 half-lives before operation, which varies depending on the type of medication; for instance, these times have been suggested to be 2-4 weeks for etanercept and 4 weeks for infliximab due to its long half-life (33, 35). The Japanese College of Rheumatology recommended to stop TNF therapy 2-4 weeks before surgery and to restart it 10-14 days after wound healing (28-31). Furthermore, based on the Nederlandse Verenigingvoor Reumatologie, anti-TNF therapy should be discontinued for four drug half-lives before surgery (28). Additionally, based on the French Society for Rheumatology, TNF therapy should be stopped for two half-lives (i.e., etanercept: 7 days, infliximab: 16-19 days, and adalimumab: 20-40 days) to five half-lives (infliximab: 40-47 days, adalimumab: 50-100 days, and etanercept: 14.5 days) before operation depending on the type of surgery (31).

The recommendations on the use of anti-TNF agents before and after surgery are different depending on the half-life of the biologic agents. For example, in a study conducted by den Broeder et al., anti-TNF therapy was interrupted for four half-lives, which is considered 39 days for infliximab, 12 days for etanercept, 56 days for adalimumab, and 3-4 weeks for infliximab (10). However, in another study, this was 1-2 weeks before operation for etanercept and 30 preoperative days for infliximab (16). Moreover, in another study, anti-TNF therapy was interrupted for 2-4 weeks before surgery for etanercept and 4 weeks for infliximab because of its long half-life (18).

Based on our findings, the appropriate time for interrupting anti-TNF agents ranges from 21 to 39 days for infliximab, 7 to 14 days for etanercept, 14 to 56 days for adalimumab, and 4 weeks for golimumab, which is dependent on the type of orthopedic surgery, patient's conditions, and drug dose regimen. Based on a study, etanercept and adalimumab were discontinued about two doses prior to surgery; however, infliximab was stopped less than one dose prior to surgery. Anti-TNF was restarted 2-4 weeks after surgery regardless of agent type and depending on the time of wound healing (6).

The occurrence of flare-ups in orthopedic patients is affected by the half-life of TNF-α inhibitors and the mechanism of action of the drug. Thus, the duration of withholding TNF blockers should be shortened in order to prevent flare-ups, although this may increase the probability of SSIs (18).

In a study carried out by Witrand, the interruption of

TNF-α inhibitors therapy more than five half-lives before operation did not cause any significant differences in the rate of adverse effects. In addition, there was no difference in terms of complications between the group discontinued TNF-α inhibitors therapy less than two half-lives and those discontinued treatment five half-lives before surgery. Anti-TNF therapy was withheld 2 weeks and 1 month before operation for etanercept and adalimumab, respectively, and it was not restarted until the complete healing (17).

Anesthetists face considerable challenges in patients with spondyloarthropathies (e.g., ankylosing spondylitis; AS), undergoing TNF therapy. Therefore, preoperative management in these patients is an issue of significant importance (36). The present study was targeted toward assessing the preoperative management of patients with spondyloarthropathies, including ankylosing spondylitis, reactive arthritis (including Reiter's syndrome), psoriatic arthritis, inflammatory bowel disease-associated spondyloarthropathy, and undifferentiated spondyloarthropathy. It is worth mentioning that this study is the first attempt investigating this issue.

Although the use of TNF-blockers, such as infliximab, in patients with spondyloarthropathy is a standard treatment, there are limited data on the optimal dosage of TNF-blockers in spondyloarthritis. Baraliakos et al. considered a dose of 3-5 mg/kg (37). Giles et al. found an association between infections complications following an orthopedic surgery and treatment with anti-TNF-α agents. However, the mentioned study was not considered in the current review as it failed to meet our inclusion criteria (21).

B-cell inhibitor: Rituximab

Rituximab (RTX) is an anti-CD20 monoclonal antibody destroying the populations of B lymphocytes. At first, it was used in combination with chemotherapy for the treatment of lymphoma. However, no significant difference was observed between the patients under RTX therapy and those undergoing chemotherapy alone in terms of the incidence of infection (38). This drug is administered to RA patients in whom anti-TNF agents are ineffective.

Hypogammaglobinemia is considered as a complication of RTX, which can lead to the development of infection (39). The literature is indicative of few surgical complications in RTX-treated patients. In a study performed by Cambridge et al., RTX-treated patients showed no increase in the rates of infectious complications; however, they demonstrated a decrease in the levels of autoantibodies, while the levels of anti-pneumococcal and anti-tetanus toxoid antibodies were stable (40). The risk of SSI after orthopedic surgery in the RA patients receiving anti-TNF therapy was similar to that in the patients under RTX treatment (13). Furthermore, the rate of postoperative complications in orthopedic surgery patients receiving anti-TNF may be the same as that in the patients administered RTX (10).

In a cohort study conducted by Godot et al., orthopedic surgery patients were infused with RTX for 12 months. They noted postoperative complications in 7.4% of the patients and estimated the rate of short-term postoperative complications to be 8.5%. They also introduced spine surgery as a risk factor for postoperative complications after RTX treatment (41).

Saech et al. reported postoperative complications in the RA patients receiving RTX. In the mentioned study, the mean interval between the last dose of RTX treatment and operation was 6±4 months. They observed no severe infectious complications or delayed wound healing in these patients. Infection was contracted only in two patients, which was not severe. Furthermore, wound healing disturbances were observed in three patients (42). These drugs can impair the immune system, thereby increasing the risk of delayed wound healing and infectious complications. However, there are insufficient data describing the exact effects of RTX on patients.

The risk of infection may increase as a result of B cell depletion therapy (43). Since skin fibrosis can be caused by intervening B cells, RTX can delay wound healing (44). Therefore, further studies should be performed to determine whether B cell depletion is a safe treatment for the patients undergoing operation. The Autoimmunity and Rituximab Registry provides data on the incidence of infection in orthopedic patients receiving RTX. Consequently, the measurement of immunoglobulin levels is a matter of fundamental importance in the high-risk patients under RTX therapy. However, the time interval between the last RTX infusion and surgery has no association with the development of complications (41).

Although the low immunoglobulin levels in some RTX-treated patients increased the risk of infection, RTX therapy is safe in patients with prior recurrent bacterial infections (45). There are limited data on the optimal timing to discontinue RTX prior to surgery and its resumption after surgery. It is recommended to interrupt RTX therapy one and half times the dosing interval and restart it after wound healing. Future studies should determine the role of other factors, such as disease activity, postoperative flare, corticosteroid use, smoking status, and diabetes, in the incidence of preoperative complications in the RTX-treated patients.

B-cell depletion in the RA patients treated with RTX can take a year. Therefore, this issue should be considered in preoperative evaluation. Accordingly, elective procedures should be postponed until the regression of B-cell count to the normal state. Nonetheless, RTX therapy should not be considered a contraindication to emergency surgery (46). In general, the effect of RTX treatment can remain for 2-3 weeks and last up to 12 months after treatment interruption (39).

T-cell inhibitor: Abatacept

Abatacept, a fusion protein of T-lymphocyte-associated antigen 4, can control the inflammatory process due to T cell activation in RA patients. This protein suppresses T cell activation via inhibiting the interaction with CD28 through binding to the CD80/86 co-stimulatory antigens (47). There is limited information on the use of abatacept during the perioperative period (48). This

drug is infused on a monthly or weekly basis through subcutaneous injection. Surgery should be performed at the end of the dose cycle (45, 49). Abatacept may lead to delayed wound healing in the RA patients undergoing orthopedic surgery (34).

In a study performed by Nishida et al., the information of seven patients who underwent orthopedic surgery was reviewed after interrupting abatacept. All the patients were treated with 500 mg/month abatacept for over 3 months. The mean of preoperative abatacept discontinuation period was nearly 16 days. In the mentioned study, no postoperative complications were observed, and SSI and delayed wound healing were noted in 1.8% and 3.1% of the cases, respectively. The administration of abatacept was interrupted between 8 days and 3 weeks before operation depending on patients' conditions. After the operation, abatacept therapy was delayed for a week after wound healing (i.e., 10-14 days). Therefore, abatacept therapy was restarted 5 weeks after the last preoperative infusion (50).

Latourte et al. reported that the rate of surgical complications was 7.2% in the patients undergoing orthopedic surgeries and treated with abatacept. In addition, they showed that the interval between the last infusion of abatacept and operation was short. Furthermore, the rate of postoperative complications showed no significant relationship with the time interval between the last infusion of abatacept and operation (51).

With regard to the high risk of serious infections in the RA patients receiving abatacept, the perioperative management of these patients is a major concern among orthopedic surgeons (48, 52). Given the high rate of serious infections during the 3 months after the first infusion of abatacept, surgery should be considered cautiously in these patients (53).

Short interval between the interruption of biologic agents and operation is associated with the risk of SSIs and delayed wound healing. On the other hand, the long-term discontinuation of these agents may lead to flare-ups in RA patients (50). Considering the 14-day half-life of abatacept, it should be stopped 2-3 weeks before surgery (54).

According to the guidelines provided by the French Society for Rheumatology, there is a paucity of information on abatacept treatment for perioperative management. Therefore, there is no comprehensive protocol for the interval between the last abatacept infusion and operation. Abatacept infusion should be interrupted based on patients' conditions, type of surgery, and severity of the disease. Based on the Japan College of Rheumatology guidelines for abatacept, the half-life of abatacept should be considered before the surgery, and abatacept therapy should be stopped before the operation. The half-life of abatacept is reported to have a range of 8-25 days with a mean value of 13.1 days. Abatacept therapy can be restarted in the absence of any postoperative complications (48).

The assessment of postoperative complications associated with various biologic agents in the patients undergoing orthopedic surgery is of great significance as these complications can affect postoperative recovery. It can be stated that all biologic agents relatively increase the risk of infections depending on their half-lives. Administration of biologic agents is suggested to be withheld two half-lives before surgery, and the clinical status of patients should be considered to restart the administration of these drugs.

It is recommended to perform further studies to examine the pre- and postoperative safety of biologic agents. Based on the results of the reviewed articles, biologic agents should be withdrawn preoperatively in patients with spondyloarthropathy. However, there is no consensus on the perioperative management of anti-TNF-α blockers and other biologic agents in these patients. Therefore, further studies are suggested in this regard.

Zahra Rezaieyazdi MD
Maryam Sahebari MD
Mandana Khodashahi MD
Rheumatic Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

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