

Review Article

Perioperative medication management of patients with Rheumatoid Arthritis

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Rheumatoid Arthritis (RA) is a chronic, systemic, inflammatory disease that is characterised by inflammation of the synovial membrane and progressive destruction of articular cartilage and bone. Furthermore, RA is often associated with extra-articular manifestations. A multidisciplinary approach is required for patients with RA in the peri-operative period. This review discusses the pre-operative, peri-operative and post-operative management of patients with RA and attempts to provide plausible answers to challenging questions that arise often when patients with RA undergo surgery. The key issues a physician has to address include controlling disease activity, assisting the wound-healing process by eliminating any delaying factors related to RA and preventing post-operative complications that may occur. The peri-operative care of patients with RA must be (strictly) personalised, given that it has to take into account a wide set of factors such as the type of surgery and the anaesthesia needed, the disease activity, the current medication the patient receives and the risk factors of co-morbidity such as age, smoking and decreased cardiac, renal, pulmonary or peripheral vascular function.

Keywords: Rheumatoid Arthritis, Perioperative management, DMARDs, TNF α , Glucocorticoids

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disorder that is characterized by synovial inflammation and hyperplasia, autoantibody production, cartilage and bone destruction and systemic manifestations, including cardiovascular, pulmonary, psychological and skeletal disorders. The worldwide prevalence of the disease is 1%, with a 3.6:1.5 ratio of female to male and its typical onset is between 30 and 60 years of age¹. The pathogenesis of the disease is not yet fully understood, but there is evidence that genetic, environmental, hormonal and immunological factors play a significant part in triggering it. Moreover, to this day there is no conclusive cure for RA and treatment administered to patients is symptomatic, although research in the past few years has given physicians reliable options to push the symptoms to recession. Newer pharmaceutical agents work by reducing inflammation and pain, preventing joint damage, and slowing the progress of the disease. More specifically over the past decade the outcomes of patients with RA have statistically improved because of access to new therapies such as biologic agents, early treatment and the new “treat to target” protocols¹⁻³.

It is reported that over 50% of patients diagnosed with

RA will undergo some kind of orthopedic surgery in the course of their lives, mainly due to the nature of the disease, causing joint destruction and deformities that lead to pain and functional loss^{1,3}. Several studies confirm a clear decrease in orthopedic surgery of the upper extremity and soft tissues of patients with RA but the rates remain unchanged for patients undergoing orthopedic surgery for total knee arthroplasty and total hip arthroplasty, although the mean age these are performed is rising¹, which in the long run could lead to a conclusion that newer therapeutic approaches are more efficient than the traditional ones. However, this raises questions about the therapeutic approach chosen shortly after the onset of the disease, which may not include Methotrexate

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or other Disease Modifying Antirheumatic Drugs (DMARDs), and instead it opts for glucocorticoids and Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)¹⁻⁴. Given the fact that in the past patients were initially treated with glucocorticoids and NSAIDs, instead of DMARDs, it remains to be seen whether newer pharmacological agents will improve timing of surgery, as well the severity of surgical procedures. This applies both to senior patients and to those who allowed the disease to progress before consulting a physician.

Choosing the right treatment for the patient is of utmost importance, as it can improve the prognosis and minimize the need for severe surgery, such as arthroplasty²⁻⁴. It is important to understand that improving the outcome of patients with RA decreases the need for severe surgery such as arthroplasty (2). Furthermore, poor outcome after surgery in RA patients could be the result of perioperative medication management decisions, which, when combined with the systemic nature of the disease, can lead to postoperative complications that are very hard to control^{1,2,5,6,13}.

Preoperative medical evaluation

Surgical procedures can be classified as a) *Acute, urgent surgery* (fractures, peritonitis, trauma) and b) *Elective surgery*, i.e., elective orthopedic surgery, Cholecystectomy.

In the first case, preoperative management is excluded due to the emergency. In the second case, preoperative evaluation should begin at least two to three weeks before elective surgery. Timely and adequate medical assessment and proper care of rheumatologic patients before surgery requires an interdisciplinary approach involving rheumatologists, orthopedics, anesthesiologists and general surgeons, so that patients receive appropriate care. Interdisciplinary collaboration can lead to the optimization of the therapeutic scheme before, during and after surgery, leading to better outcomes of the overall treatment⁷.

Several tests can be held to contribute to the proper management of patients undergoing surgery. These include *lab tests*, such as complete blood count, urinalysis and urine culture, blood group and cross- linking coagulation factors (INR, APTT, PT), electrolytes concentrations, serum, creatinine, speed erythrocyte sedimentation rate (ESR), C Reactive Protein (CRP), and *scanning tests*, which include radiography of the affected joint, electrocardiogram, radiography test i.e. thoracic X-ray, and lung function tests that include blood gases⁵⁻⁷.

Full medical history must be taken before surgery. During the physical examination, it is very important to evaluate the cardio-respiratory status, and other organ involvement, but it is also important to note the musculoskeletal involvement in planning the way the patient is positioned on the table for the procedure. In order to ensure patients' safety during the procedure, anesthesiologists must consult and agree with the surgeon and the rheumatologist regarding optimal position of the head and cervical spine⁸.

To prevent complications in the perioperative period,

such as post-operative infections, appropriate measures before surgery should be strongly advised including good oral hygiene and weight loss and physiotherapy⁶.

Cardiovascular risk evaluation

It is well known that patients with RA have a higher risk of cardiovascular disease than the general population. Inflammation may attack the synovium and damage the blood vessels lining, forming plaque, which narrows the arteries and thus raises blood pressure and reduces blood flow. Plaque can be brittle and prone to rupture, increasing the risk of deep vein thrombosis and pulmonary embolism, among others. It is also reported that RA patients have an increased risk for atrial fibrillation. In fact, several studies report that RA patients manifest similar risk for cardiac disease as patients with diabetes^{6,7,9}.

It is also reported that these patients often have anemia due to the disease or as a side-effect from drug therapy and the high probability of a needed blood transfusion during the operation must be taken under serious consideration.

Cervical spine evaluation

RA can involve important cervical spine implications, which can influence the perioperative management, especially the positioning for anesthesia. Affected cervical vertebrae (most commonly A1- A2), could present instability, creating important problems concerning the position of patients during the surgical procedures. Symptoms such as neck pain or neurological deficit may derive from cervical spine disease and must be investigated with flexion and extension radiographs and, if deemed necessary, MRI scans. There is a substantial risk for spinal involvements, especially in severe cases, which include the atlantoaxial joint and the subaxial cervical spine as the sites that are most commonly affected by RA¹⁰.

In addition, close cooperation is necessary between rheumatologists, general surgeons, spine surgeons and anesthesiologists to provide the best care possible^{6,8,9}.

Medication management

This section attempts to provide a concise report of medication administered to patients with RA and their possible association with post-operative complications. Due to the complex nature of the autoimmune disease, currently there is no consensus on specific drug administration protocols during the pre-operative, inter-operative and post-operative period. The drugs included in this section, will be categorized into four distinct groups, as follows: i) Traditional non- biologic Disease Modifying Antirheumatic Drugs (DMARDs), ii) Biologic DMARDs, with two subsequent categories: a. Anti-Tumor Necrosis Factor alpha antagonists (anti-TNF α) and b. Biologic DMARDs, other than TNF α , iii) Medication co-administered with DMARDs, sub-categorised in to three groups: a. Glucocorticoids b. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and c. Osteoporosis Therapy and finally iv) Antibiotics Prophylaxis.

Medication	Pharmacologic t ½	Dosing interval	Preoperative withhold	Continue
Methotrexate (MTX)	3-15 hours, dose dependent	weekly	none	Yes
Leflunomide	14 days	daily	2 weeks	No
Hydroxychloroquine	32-50 days	daily	none	Yes
Azathioprine	5 hours	daily	5-7 days	No
Sulfasalazine	7-15 hours depended on acetylation rate	daily	5-7 days	no

Table 1. Perioperative medication management recommendations for DMARDs in use for therapy of RA.

Medication	Pharmacologic t ½	Dosing interval	Preoperative withhold	Continue
Etanercept	3-5.5 days	weekly	2 weeks	no
Adalimumab	10-20 days	2 weeks	2-4 weeks	no
Infliximab	7-12 days	4-8 weeks	6 weeks	no
Golimumab	7-20 days	monthly	6 weeks	no
Certolizumabpegol	14 days	2 weeks	6 weeks	no
Tocilizumab	sc: 5-13 days iv: 11-13 days	sc: weekly iv: monthly	sc: 3 weeks iv: 4 weeks	no
Abatacept	13-14 days	sc: weekly iv: monthly	sc: 2 weeks iv: 4 weeks	no
Anakinra	4-6 hours	daily	?	?
Tofacitinib	3 hours	daily	?	no

Table 2. Perioperative medication management recommendations for biologic DMARDs in use of therapy of RA.

I. DMARDs (Table 1)

Hydroxychloroquine

It is an antimalarial drug which works by impairing neutrophil chemotaxis and impairs complement-dependent antigen-antibody reactions. There is limited data regarding the perioperative risk of infection or other side effects. There have been two studies that did not show an association between hydroxychloroquine and infection. Clinical based evidence recommends continuation of Hydroxychloroquine in the perioperative period^{1,9}.

Methotrexate (MTX)

This drug is considered the cornerstone of the treatment of RA. It is a Dihydrofolate Reductase (DHFR) inhibitor which increases adenosine release, inhibits lymphocyte proliferation (folate antagonist) and modulates cytokine profile. The majority of studies indicate the safety of MTX in the perioperative period and continuation reduces the risk of rheumatoid arthritis flare. However, in patients with type 2 diabetes not controlled by drugs or patients receiving prednisone at a dose greater than 10 mg/day and major surgery, it is recommended to discontinue MTX for one week

and follow-up one week after surgery. It is also necessary to monitor the liver function because methotrexate can cause serum aminotransferase elevations and long term therapy has been linked to development of fatty liver disease, fibrosis and even cirrhosis^{1,9}.

Leflunomide

Leflunomide is an immunomodulatory drug which inhibits pyrimidine synthesis and also demonstrates anti-inflammatory and anti-proliferative effects. The data for this drug are contradictory. Some clinical evidence suggests that the drug does not inhibit the recuperation process after surgery and therefore there is no need for it to be discontinued before surgery^{11,12}. On the other hand, another study recommends that it be withheld for two weeks prior to surgery and resumed three days after^{1,9}.

In a study with patients who underwent elective orthopedic surgery there was little evidence suggesting that continued treatment with Leflunomide was associated with a higher risk of delayed wound healing. There have also been studies reporting that there is not statistical difference of infections occurring post-operatively between those who discontinued Leflunomide and those who didn't¹³.

Azathioprine and Sulfasalazine

Azathioprine is an antagonist of purine metabolism and may inhibit the synthesis of RNA and DNA. It can also interfere with cellular metabolism and can inhibit mitosis. Sulfasalazine is a 5-Aminosalicylic acid and can modulate inflammatory response, especially leukotrienes or TNF-inhibitors (Tumor Necrosis Factor- inhibitors). These drugs are associated with leucopenia and it is recommended to discontinue 5-7 days prior to surgery and resume one to two weeks after surgery^{1,9}.

II. Biologic DMARDS (Table 2)

a. Anti -TNFa (Tumor necrosis factor alpha antagonists)

Conflicting data are available regarding the perioperative use of anti-TNFa. In multiple studies, anti-TNFa was associated with post-operative complications such as infections and delayed wound healing. Studies comparing DMARDS and TNF inhibitors suggest a link between anti-TNFa administration and increased risk of surgical site infection compared to standard DMARDS. TNFa inhibitors are associated with a higher risk of opportunistic infections, due to their ability to stop some necessary cell procedures regarding their response to inflammation and, therefore, immunity. Whereas, some researched argue that for minor procedures, withholding most of those agents is not necessary because there is no evidence of impaired healing³, there's enough published data that showcase the risk of such implications in major procedures^{1,14}.

Meta-analysis suggests anti-TNFa may raise the risk of infection, delayed wound healing and flare eradication^{2,14}.

Clinical based evidence suggest that it should be discontinued for the duration of 1-1.5 half-life, since a longer period of discontinuation, such as 3-5 half-life of the drug, may lead to increased risk of infection after elective surgery and disease eradication, manifested predominantly with flares. Specifically, the approach to perioperative use of anti-TNFa is to allow for at least one to two treatment cycles without drug administration prior to surgery, and resume administration once the external wound healing is completed and there is no evidence of serious infection^{1,2,6,15,16}.

The types of anti-TNFa currently used include, *Etanercept* a recombinant human tumor necrosis factor receptor (p75) which should be withheld for one to two weeks prior elective surgery^{1,2,15,16}. *Adalimumab*, a fully human anti- tumor necrosis factor a monoclonal antibody, which is recommended to be withheld for two to four weeks prior to surgery^{1,2,15,16}. *Golimumab*, a human anti-Tumor necrosis factor a IgG1 monoclonal antibody^{1,2,15,16}, and *Infliximab*, a chimeric anti-tumor necrosis factor a monoclonal antibody should both be left out of the treatment regime six weeks prior to surgery^{1,2,15,16}. Finally, *Certolizumab pegol*, an anti-TNF distinct from the others in terms of its structure because it is a recombinant Fab' antibody fragment against tumor necrosis factor alpha. For this drug recommended discontinuation also reaches up to six weeks prior to surgery^{1,2,15,16}.

b. Biologic DMARDS other than TNFa

Tocilizumab

It is a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R). In a retrospective study of 161 orthopedic surgical patients, there were 20 cases of delayed wound healing and 3 cases of infection. Infection diagnosis could be quite difficult, since that the level of CRP is not always increased in patients taking tocilizumab and that could lead to a delay in taking the appropriate therapeutic measures during recuperation. It is suggested to discontinue the drug three weeks prior to surgery for the subcutaneous injection and a month for the i.v. infusion prior surgery^{1,2,15,16}.

Abatacept

It is a human fusion protein of CTLA-4 and immunoglobulin and it is not associated with the risk of infection or delay of wound healing. Abatacept is administered as a weekly subcutaneous injection or as a monthly infusion. It is recommended to schedule surgery at the end of the dose cycle^{1,2,15,16}.

Rituximab

It is a monoclonal antibody against CD20 B cell antigen. The recommended dosage of Rituximab for RA consists of one intravenous infusion followed by a second infusion two weeks later every 6 months. Therefore, elective surgery should be scheduled at a reasonable time within the semester, after B-cells count returns to normal. Preoperative screening of immunoglobulin levels is recommended and surgery should be scheduled when B-cells return to circulation. In non- elective surgery, it is not possible to wait for the levels of B-cells to normalize when surgery is an emergency^{1,2,15,16}.

Anakinra

It is an interleukin-1 receptor antagonist. Trials showed that the infection rate was similar to the patients receiving placebo. Therefore a caution approach is recommended^{1,6,15-17}.

Tofacitinib (anti-Janus-Kinase 3)

This orally administered drug is a new addition to the list of medications used in RA patients. In the trials tofacitinib is associated with neutropenia, anemia and upper respiratory infections. The data available for does not lead to safe conclusions, enough to make recommendations for this drug's perioperative administration

III. Medication co- administered with DMARDS

a. Corticosteroids

Prolonged use of glucocorticoids may suppress the hypothalamic-pituitary-adrenal (HPA) axis and during periods of stress, such as surgery, production in endogenous cortisol may not occur. The use of "stress dose" of glucocorticoids has become a common perioperative practice for patients receiving glucocorticoid therapy. However, the current

approach is to determine the history of glucocorticoid therapy as well as the type and duration of surgery planned¹⁷.

It must be taken into consideration that patients under chronic glucocorticoid therapy are at a higher risk of presenting various problems in the perioperative period such as: increased risk of infections, ulcer, fracture, gastrointestinal hemorrhage^{18,20} impaired wound healing²¹ and increased skin friability.

Acute side effects that can influence surgical outcome in high-dose administration of glucocorticoids are: fluid retention, hyperglycemia, hypertension, and increased risk of infection.

All RA patients undergoing surgery should be thoroughly examined for a possible HPA axis suppression²¹⁻²³.

Evaluating HPA axis suppression: Morning serum cortisol before 8 am (24 hour off glucocorticoid replacement dose) is a good screening method for evaluation of Secondary adrenal insufficiency

- An early morning cortisol value of less than 5 mcg/dL (138 nmol/L) suggests an HPA axis suppression that needs additional glucocorticoid intake perioperatively.
- If cortisol is more than 10 mcg/dL (275 nmol/L), the patient probably does not have a significant suppression of the HPA axis and could continue with his current glucocorticoid treatment on the day of surgery.
- If early mornings cortisol is between 5-10 mcg/dL (138-275 nmol/L) further investigation is required with ACTH corticotrophin stimulation test or empiric additional treatment with glucocorticoid prior surgery. The ACTH stimulation test consists of measuring morning serum cortisol 30 minutes after having administered 250 mcg of ACTH. A cortisol level more than 18 mcg/dL (497 nmol/L) has no need for additional glucocorticoid therapy perioperatively. A cortisol level less than 18 mcg/dL signifies that patients show an inadequate response and should receive glucocorticoid medication prior to surgery.

Patients who have been taking any dose of glucocorticoids for less than three weeks, or less than 5 mg/day or its equivalent (4 mg/day of methyl prednisone or 20 mg/day of hydrocortisone) for any length of time or patients who has been taking less than 10 mg/day of prednisone every other day, usually do not require "stress doze" of corticosteroids. On the other hand, it is suggested that patients who receive glucocorticoids and show clinical Cushing's syndrome or any patient who is taking more than 20 mg/day of prednisone or its equivalent for more than three weeks, must be treated with supplemental glucocorticoids in the perioperative period²⁰.

In patients who fall in the *intermediate category* (HPA suppression unknown) evaluation of HPA axis suppression before surgery is highly recommended.

Another point which showcases the importance of taking a good medical history before proceeding with diagnosis or treatment, is the long- term effect of glucocorticoid use that may suppress the HPA axis, as long as year after the discontinuation of the treatment. Studies have shown that

HPA axis suppression could take up to one year to be fully reversed after the discontinuation of glucocorticoids. For patients, who used glucocorticoids in the past year but now are currently off, an HPA axis evaluation is recommended, if their regimens included a higher dosage or a dosage administered for a longer period of time, that those that could potentially suppress the HPA axis. Assessment is done through morning serum cortisol, as described above.

Also, patients using topical and inhaled glucocorticoids, should be examined for HPA axis suppression if the daily dosage of fluticasone exceeds 750 mg for a period longer than three weeks and if that therapy was given less than three months before the date of surgery. Last group of patients that should be checked for HPA axis suppression are those who had intra-articular injections to treat localized pain in a joint (chronic or acute), but only in case where the number of shots exceed a total of four injections and they had it done less than three months before surgery²¹.

Emergency surgery: For patients who fall into intermediate category and have to do an emergent surgery, it is recommended to receive empiric perioperative glucocorticoid coverage. For minor procedures the patients' takes the usual morning steroid dose and no extra supplementation is necessary. For moderate surgical stress is given 50 mg hydrocortisone intravenous just before the procedure and 25 mg of hydrocortisone every 8 hours for 24 hours. For major surgical stress is given 100 mg of intravenous hydrocortisone before procedure and 50 mg every 8 hours for 24 hours²⁸.

b. NSAIDs

They are currently included in the 2012 ACR recommendations of treatment for Rheumatoid arthritis as well as for the management of osteoarthritis of the hip and knee. It is well known that the use of NSAIDs is associated with the risk of renal, cardiac, and vascular toxicity. Patients with RA are using NSAIDs in order to relieve the pain. But the preoperative use involves the risk of bleeding, cardiovascular risk, risk of decrease in bone fusion rates and possibly poor integration of the bone prostheses¹³.

Studies have shown that the continuation of NSAIDs up to the time of surgery may increase significantly the risk of hemorrhage. This particularly applies to nonselective NSAIDs, such as the use of cyclooxygenase-2 (COX-2)-selective NSAIDs. Specifically the use of indomethacin was associated with 17% more blood loss than meloxicam²². The use of diclofenac was associated with 32% more blood loss than rofecoxib and Ibuprofen with 45% greater blood loss²⁷.

The NSAIDs are also used postoperatively for pain management and to lower the dosage of narcotic treatment. Another use of NSAIDs is to prevent heterotopic ossification, with new bone formation at the side of surgical trauma that could lead to functional limitation and more pain. Additionally, studies have shown that the use of NSAIDs is allowed for short-term pain relief after arthroplasty without concern for bone in growth inhibition in non-cemented prostheses.

c. Osteoporosis Therapy

Most patients with RA are treated, and with good reason, for osteoporosis. In the past, estrogens were frequently used as a treatment for osteoporosis. Those patients had to discontinue their osteoporosis therapy before surgery, due to higher risk of thromboembolic events. The same concerns the use of tamoxifen and raloxifene²⁹.

The cornerstone of osteoporosis treatment are *Bisphosphonates* and therefore patients with RA frequently list them among their preoperative medications¹⁷. As it is, bisphosphonates can be administered orally, once the patient is able to stand erect or sit on the bed in an upright position, as soon as that is allowed by the surgeons³⁴.

IV. Antibiotics Prophylaxis

Antibiotic prophylaxis is an imperative for patients with RA patients, who undergo lengthy procedures, in order to prevent surgical site infections. Special care should be given to patients who are scheduled for a knee or hip replacement or are going to receive a prosthetic joint. In addition, RA patients are at a high risk of bacteremia when the surgical procedure takes place in an already infected area. ACR recommends cefuroxime or cefazolin, as the drugs of choice, and should be administered 30 to 60 minutes prior to the first incision³³. If the person has beta-lactam allergy, the use of vancomycin or clindamycin two hours before incision is recommended. In addition, if there's a fear of pathogen infection other than staphylococci and streptococci, additional agents should be given consideration. As far as it concerns surgical repair of closed fractures, wound infection can be prevented with the use of a single dose of cephalosporin, and the antibiotic prophylaxis should be stopped 24 hours after surgery. Prophylaxis is also necessary if there is a great blood loss during the procedure or if the procedure is prolonged^{3,31}. The latest EULAR recommendations for drug agents in RA do not include antibiotic prophylaxis in case of surgery³⁵.

Postoperative follow up

To reduce the risk of postoperative complications of patients with RA, medical evaluations should be done according to a protocol, determined by the careful analysis of possible risks of postoperative complications. For this reason it is recommended to monitor and evaluate meticulously the risks of infection, of venous thromboembolism and pulmonary embolism, as RA patients have a greater risk for such these complications following surgery^{3-5,14,31,32}. Specifically, evidence shows that patients with RA suffer greater rates of prosthetic joint infections in comparison to those diagnosed with osteoarthritis. The risk is increased even more in the setting of revision arthroplasty and previous prosthetic infection^{2,32}.

According to a case control study of patients treated with TNF- α inhibitor therapy, *Staphylococcus* was the most likely infectious cause of total joint arthroplasty infection. In multivariate analysis, the use of prednisone and primary

arthroplasty or revision within the previous year were indicative of serious risk factors for infection. A meta-analysis showed that patients with RA have a higher risk of dislocation compared to osteoarthritis patients, in case of total hip arthroplasty⁹.

Physical therapy is usually recommended for RA patients after surgery (33, 34) not only for faster rehabilitation and engagement in "activities of daily living", but for pain management as well.

Patient education

Allowing RA patients to have a better understanding of their disease and the therapeutic approaches advised for them, is key to empower them in order to control active inflammation and other symptoms, and to reinforce patients' functional and psychological well-being. Physicians should inform the patients preoperatively for the possible postoperative complications, including full disclosure of risks, benefits and alternatives.

Patients should be given both written and verbal information, including answers to their own questions, regarding the procedure, the specific type of anesthesia recommended, their postoperative physical therapy regime, as well as pain management after the surgery. Prior to surgery, it is highly recommended for patients to have an understanding regarding: the pain control plan, the expected duration of the surgery, the expected duration of inhibitions in the motor skills, the physical activity program following surgery, and the importance of early mobilization^{5-7,9,33,34}.

Conclusions

This paper's scope is to cover perioperative drug administration treatment of patients with RA. Patients with RA require special attention because of their disease, treatment and comorbidity in the perioperative period. Successful perioperative management requires a multidisciplinary approach including orthopedic surgeons, rheumatologists, anesthesiologists and radiologists. RA is a disease that requires long-term treatment and therefore appropriate psychological support. Many new treatments have been developed over the last years that aim to lower inflammation and pain, prevent joint damage, and slow the progress of the disease.

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