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TREATMENT AND MANAGEMENT OF RHEUMATOIDARTHRITIS

K.Nag Hari Krishna*[1], B.Meghana[2], G.Mercia Rani[2], K.Anitha[2], A.Jagadeesh[3], M.Jalaiah[3]

[1] Department of Pharmacology, QIS College of Pharmacy, Vengamukkapalem, Ongole, Andhra Pradesh, India.

[2] Research scholar, B.Pharmacy, QIS college of Pharmacy, Vengamukkapalem, Ongole, Andhra Pradesh, India.

[3] Department of Pharmacolgy, QIS College of Pharmacy, Vengamukkapalem, Ongole, Andhra Pradesh, India.

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Abstract

Rheumatoid arthritis is an autoimmune inflammatory disease characterized mostly by synovitis, which is frequently Clinical manifestations include fever, malaise, edema, pain, and stiffness in several joints are followed with extra-articular organ involvement, such as interstitial pneumonia. After the initial stage, joint degradation progresses swiftly, and once the afflicted areas' deformed joints are obvious, physical dysfunction that cannot be reversed begins to occur. Thus, precise diagnosis and Treatment is required from the moment the problem first appears. While anti-inflammatory drugs and glucocorticoids were used as palliative care, disease-modifying anti-rheumatic drugs (DMARDs) are currently used to slow down and control the advancement of sickness and immunological diseases. By maintaining remission, these drugs have also been shown to halt the advancement of joint degradation and physical disability over a prolonged period of time. Precision medicine, safer and more effective treatment techniques targeted at drug holidays or cures, and therapeutic strategies are some of the future developments in medicine.

***Corresponding Author**
K. Hari Krishna

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Introduction

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an inflammatory autoimmune joint disease that mostly affects symmetric joints. It is more common in women than males and is usually diagnosed in older adults. Rheumatoid arthritis is a multisystem and polyarthritis condition. It is an autoimmune disease of the synovial membrane that prevents the release of cytokines that exacerbate inflammation, resulting in a persistent inflammatory state. The body's immune system attacks the robust membrane lining of the joints, which encircles all splinters, starting with the synovium and peripheral joints [1-5]. In individuals with RA, ultrasonography abnormalities include tendon sheath broadening, tendon rips, joint space widening, synovium hypertrophy, fluid buildup, bone erosions, and cartilage deformities. Persistent non-supportive swelling of the synovial joints is the criteria of Rheumatoid Arthritis (RA), as established by the American College of Rheumatologists in 1987. With all of this joint depletion, deformities and bone roughness progress, frequently causing the patient some searing discomfort [6]. Rheumatoid arthritis is the only immunologic marker for the disease that has been identified to far. Rheumatoid factor (RF) levels in the blood have been linked in 80–85% of RA patients to increased disease activity, radiographic progression, and the onset of extra-articular symptoms. Within the range of 50-90% and 50-95%, respectively, are the RF sensitivity and specificity values. A poor prognosis and early joint deterioration are correlated with serum levels of anti-CCP [7] All of this joint depletion causes deformities and bone junction, which can be very unpleasant for the sufferer. Although the primary cause of RA is still unknown, research indicates that genes, hormones, and environmental factors are responsible. These factors include obesity, infectious diseases caused by bacteria and viruses, women's hormones (70 percent of RA patients are female), and women's hormones. Exposure to silica, mineral oil, pesticides, and cigarette smoke at work are some other causes of environmental factors. Desorption of bone can occur from smoking. In those who have osteoporosis, this may speed up the disease's progression. It also causes women's estrogen levels to drop, which may accelerate menopause and worsen bone loss [8]. The prevalence of RA in India's adult population is estimated to be 0.75 percent. Rheumatoid arthritis is a worrying condition that affects more people than just the world's population. Over the past 10 years, the treatment of RA has undergone a huge revolution, with the majority of patients

seeing considerably improved clinical results thanks to the discovery of biologics and other target treatments, as well as more aggressive and early therapeutic strategies including treat-to-target. Since new pharmacological medicines and other innovative therapies, such biologics, have recently developed for the treatment of RA, the primary goal of the analysis is to analyze RA therapeutic options in the modern period [9].

Etiology

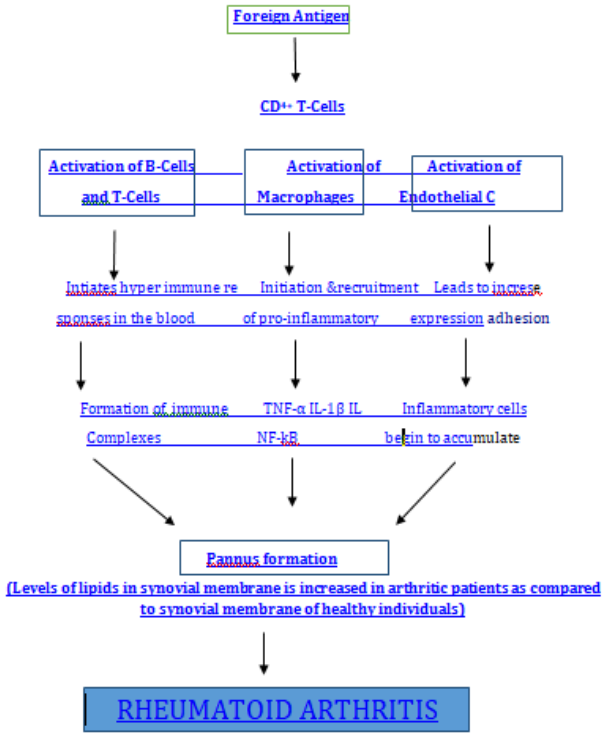
It is thought that RA is caused by a confluence of environmental and genetic variables. Men under 30 are more vulnerable and have more severe effects. Compared to men, women are more vulnerable to the illness [/30] Seronegative RA heritability is lower than seropositive RA heritability, which varies from 40% to 60%. The study of heritable alterations that take place without changing the DNA sequence is known as epigenetics. These chromatin or DNA changes include DNA methylation, histone tinkering, and non-coding RNA-mediated control [10]. Smoking and shared epitope (SE) have been shown to raise the risk of rheumatoid arthritis in individuals with anti-CCP (anti-citrullinated protein antibody) positive.The factor or variables that cause rheumatoid arthritis (RA) to develop or worsen have piqued interest. In addition, investigators for decades were eveded. One prevalent theory has been an infectious origin [11].

Epidemiology

Rheumatoid arthritis (RA), twice as frequent in women as in men, is thought to affect 0.24 to 1% of the population. While there is a possibility of various adverse long-term repercussions, the use of more rigorous treatment programs and robust pharmaceutical regimens has helped to partly limit them. Frequency and Incidence Around the world, 0.24 percent of people suffer from RA, according to the Global Burden of Disease 2010 Study. The average prevalence of RA is estimated to be between 0.5 and 1 percent, with higher estimates seen in the United States and northern European countries. The yearly incidence of RA is estimated to be 40 per 100,000 persons in the United States and northern European countries[12]. Most research on RA epidemiology has been done on people in northern Europe or America. Consequently, the majority of epidemiologic estimates of RA and the identification of risk factors come from these groups. In some communities, the incidence and prevalence of RA are significantly greater, with rates up to ten times higher than in most other demographic groups (Pima Native Americans, for example). Women are twice as likely as men to acquire RA, with their incidence and prevalence rates being higher. Men have a 1.7% lifetime chance of developing RA, while women have a 3.6% risk [13].

Pathophisiology

The human leukocyte antigen D-related B1 gene (HLA-DRB1) is the most pertinent disease-suspectible gene discovered from genome-wide study of single nucleotide polymorphisms in rheumatoid arthritis patients. Other disease-suspectible genes were also found. TNF alpha-induced protein 3 (TNFAIP3), cytotoxic T-lympocyte antigen-4 (CTLA4), signal transducer and activator of transcription 4 (STAT4), C-C motif chemokine ligand 21 (CCL21), and peptidyl arginine deiminase 4 (PADI4) genes are among them [14]. In the synovial tissues of rheumatoid arthritis patients, autoreactive T and B lymphocytes gather.T cells have an immune tolerance to autoantigens; however, when this tolerance is compromised, autoreactive T cells become activated and encourage B cells to produce autoantibodies. Autoantibodies and antigens combine to generate immunological complexes that are deposited in tissues and induce histological damage by activating complement (type III allergies).Angiogenesis or vasodilation, synoviocyte proliferation, and lymphocyte accumulation are the characteristics of tissues with synovitise .Lymphoid follicle- and germinal center-like structures can arise from the accumulation of memory T and B cells in tissues with widespread inflammation. Close cellular contacts are seen in these structures, where co-stimulators and proinflammatory cytokines are strongly expressed [15]. TNF, interleukine (IL)-1, and IL-6 are examples of the inflammatory cytokines that are produced in great quantities by lymphocytes and synoviocytes in synovitis lesions and are responsible for the disease's development. Along with systemic symptoms including malaise and low-grade fever, extra-articular organ involvement such interstitial pneumonia, sialadentis, and kerato-conjunctivitis sicca is frequently seen. Furthermore, synoviocytes triggered by cytokines release matrix metallooroteinases (MMP) into the synovial fluid. These enzymes facilitate the breakdown and absorption of cartilage. Furthermore, in order to trigger the maturation and activation of osteoclasts, synoviocytes and lymphocytes express receptor activator of nuclear factor-kappa B ligand (RANKL)»16.TNF, interleukine (IL)-1, and IL-6 are examples of the inflammatory cytokines that are produced in great quantities by lymphocytes and synoviocytes in synovitis lesions and are responsible for the disease's development. Extra-articular organ involvement, such as low-grade fever and malaise, in addition to systemic symptoms [16]. Till they come into touch with the bones, proliferative and stratified synoviocytes seen in inflammatory granulation tissues continue to proliferate. Mostly at the site of contact, multinucleated osteoclasts break down and absorb bone, destroying joints.



Symptoms

The effects of rheumatoid arthritis vary throughout individuals. Long-term joint difficulties are experienced by certain individuals. The symptoms of rheumatoid arthritis advance more quickly in others. Remissions are often followed by symptom flare-ups for many individuals.

Several joints may feel uncomfortable, edematous, stiff, and painful when suffering from rheumatoid arthritis.

- Stiffness, especially in the morning or during extended periods of sitting.
- The same joints hurt and become stiff on both sides of your body.
- Tiredness or weariness, fever, weakness, aches, swelling, and redness in the joints.
- Among the additional symptoms are
- Fatigue, which is defined as being exhausted and lacking in energy.
- not feeling hungry or having a weak appetite
- Frequent perspiration, fever, weight loss, and elevated temperature.
- a condition where inflammation causes dry eyes
- Inflammation-related chest discomfort.
- All joints in the body can be impacted by rheumatoid arthritis, however it often manifests in the hands and feet's tiny joints initially. The majority of the time, both sides of the body is impacted in the same manner and at the same time, not always.
- Rheumatoid nodules, which are fleshy lumps that grow beneath the skin surrounding afflicted joints, occur in few persons. While occasionally unpleasant, they are often.

Cause

1.**Age:** Patients with rheumatoid arthritis can be diagnosed at any age, although most do so between the ages of 40 and 60. Approximately 75% of those with rheumatoid arthritis are working age when they are initially diagnosed.

2. Sex: Women have rheumatoid arthritis two to three times more frequently than males do.

3. Genetics: Rheumatoid arthritis is caused by a confluence of environmental and genetic variables, including diet and smoking. Although the hereditary component of the ailment is unknown, having a relative with the condition is likely to raise your risk of getting it.

4. Weight: Compared to those who are of a healthy weight, those who are overweight have a much higher risk of having rheumatoid arthritis.

*Using your height and weight, the body mass index (BMI) determines if your weight is healthy. An optimum BMI range for most individuals is 18.5 to 24.9.

*Should your BMI be:

- If your weight is less than 18.5, you are underweight.
- If your weight is between 18.5 and 24.9, you are in the healthy zone.
- If your weight is in the range of 25 to 29.9, you are overweight.
- If you fall between 30 and 39.9, you are considered obese.

5. Smoking: Smoking cigarettes raises your risk of rheumatoid arthritis by a considerable amount. Go to the Smoke free website if you want to give up smoking.

6. Diet: Research suggests that consuming a high red meat diet and low vitamin C intake may raise the chance of getting rheumatoid arthritis.

Diagnosis of Rheumatoid Arhtritis

Medical History

- About your symptoms, when and how they started, how they have changed over time.
- What limitations in activities may have, such as difficulty with work, leisure, or activities around the house.

Physical Examination

- Checking the joints.
- Observing others as they move, bend, and do daily tasks
- Examining the skin for nodules or rash.
- Paying attention to the chest for indications of lung inflammation.

Laboratory Tests

Rheumatoid factor (RF): This blood test looks for the RF antibody, which many people with rheumatoid arthritis may ultimately have in their blood. An antibody is a special type of protein produced by the immune system that usually helps the body fight against invaders. Not every patient with RA will test positive for RF; some may test positive but not have RA, and some may test positive but have another condition. Nonetheless, when paired with the results of further tests and evaluations, this test can be utilized by physicians to diagnose rheumatoid arthritis.

Anti-cyclic citrullinated peptide antibody, or anti-CCP: This blood test looks for anti-CCP antibodies, which are often found in rheumatoid arthritis patients. Furthermore, anti-CCP may appear before RA symptoms do, which might help with an early identification of the illness. When used in conjunction with RF blood testing results, this test is quite beneficial in verifying a diagnosis of rheumatoid arthritis. It is important to remember that some people with normal blood tests might nonetheless have rheumatoid arthritis.

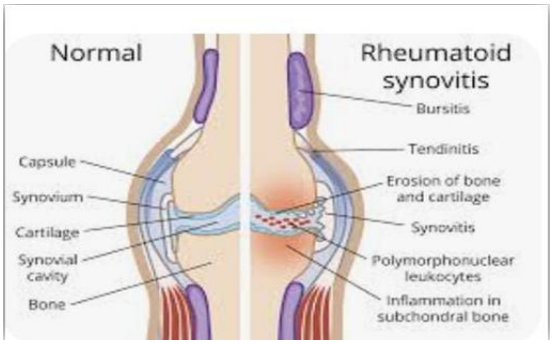
whole blood count:-This blood test can assist in the diagnosis of anemia, which is frequent in RA patients, by measuring various blood cell counts.

Erythrocyte sedimentation rate: This test tracks the progression of a disease and how well a therapy is working by measuring inflammation in the body.C-reactive protein: This common test for inflammation can be used to diagnose rheumatoid arthritis, monitor the illness's course, and assess how well therapy is working.

Additional blood tests: To evaluate overall health and rule out other conditions, the doctor may also run additional tests to examine electrolytes, liver, thyroid, muscle, other autoimmune, and infection indicators. Other tests specific to rheumatoid arthritis are occasionally considered.

Treatment of Rheumatoid Arthritis:

• NSAIDs have the ability to both reduce inflammation and ease pain.

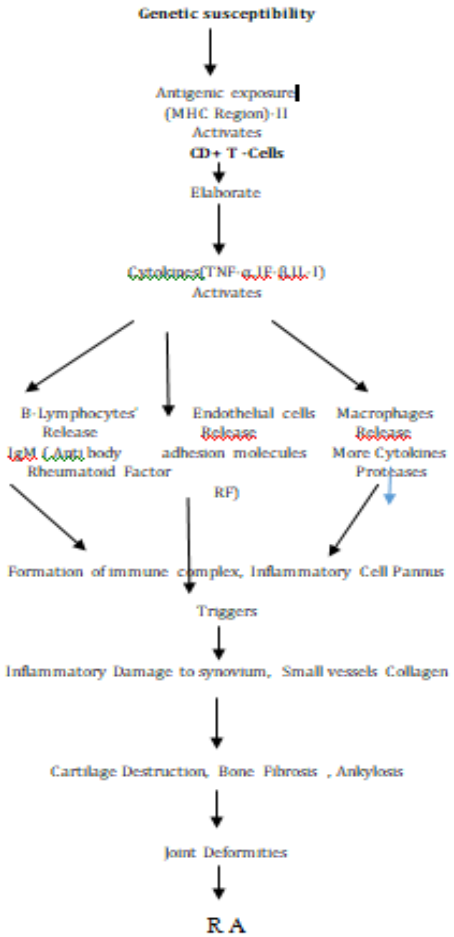


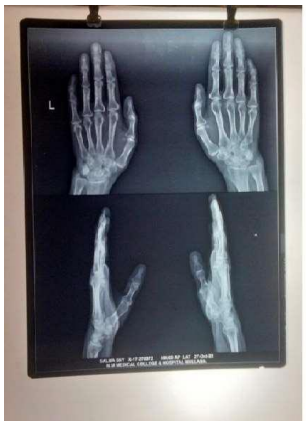
Steroids: Drugs called corticosteroids, such prednisone, lessen inflammation and delay joint deterioration.

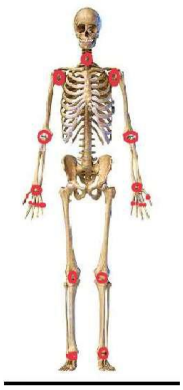
- **Conventional DMARDs:** these medications can prevent irreversible damage to the joints and other tissues by slowing the course of rheumatoid arthritis. Methotrexate, leflunomide, hydrochloroquine, and sulfasalazine are examples of common DMARDs.

Although they vary, side effects might include serious lung infections and liver damage.

- **Biologic agents:** often referred to as biologic response modifiers, this more recent family of DMARDs consists of tocilizumab, adalimumab, abatacept, rituximab, and sarilmab.
- The best results from biologic DMARDs are typically obtained in combination with a traditional DMARD, such methotrexate.The danger of infections is also increased by this kind of medication.
- **Targeted synthetic DMARDs:** in the event that biologics and traditional DMARDs prove ineffective, baricinib and tofactinib may be utilized.







Treatment Goals

When a doctor prescribes medication to a patient for therapy, there are a few important goals that must be met. These include:

- The primary objective is to manage the symptoms, such as inflammation and discomfort.
- Preventing the condition from causing harm to the joints and other structures.
- To lessen the patient's capacity for RA and support the preservation of appropriate joint mobility and quality of life.
- The other is to lessen the patient's long-term problems and increase joint mobility over an extended length of time.

First-line treatment

NSAIDs AND Corticosteroids

General pain relief and inflammation reduction are the goals of first-line treatment. The two primary goals of first-line treatment are pain alleviation and decreased inflammation. Ibuprofen (Advil, Motrin), ketorolac (Iodine), and non-steroidal anti-inflammatory medicines (NSAIDs) are examples of fast-acting remedies. Aspirin's ability to reduce prostaglandins makes it a potent anti-inflammatory when used in big quantities for many conditions. One of the earliest NSAIDs for the treatment of joint pain was this one. Aspirin overuse can result in a variety of adverse side effects, such as tinnitus, hearing loss, and upset stomach. More recently introduced to the market, NSAIDs are just as effective as aspirin but also require lower daily amounts of medicine. Anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase, which prevents the production of prostaglandins, thromboxane, and prostracin. Gastritis, stomach pains, ulcers, and other typical side effects [17].

Corticosteroids:

These medications are more effective than NSAIDs in lowering inflammation, but they also have more side effects. As such, they are only used in small dosages and for short periods of time during RA flare-ups or exacerbations. The symptoms of local inflammation may be treated with corticosteroid injections administered intra-articularly. These steroids function by decreasing eosinophil activity via inhibiting the production of phospholipids that decrease inflammation. As adverse effects, these medications may include immunosuppression, diabetes, weight gain, and weakening of the bones. To stop bone weakening, the patient is therefore recommended to take calcium and vitamin D supplements. When the patient's condition has improved, the dose can be

gradually reduced to reduce side effects. the constant dose. It is important to avoid abruptly stopping a continuous steroid dosage as this might lead to RA flare-ups or inhibition of the hypothalamine-pituitary-adrenal axis (HPA) [18].

Opioid Analgesics

Opioids such as codeine, dextropropoxyphene, and tramadol have the potential to be helpful in the short term for managing rheumatoid arthritis pain, but the hazards outweigh the benefits.They suggest starting with other analgesics. A recent Cochrane review that comprised 11 studies with 672 patients meeting the necessary quality standards was released. from these research Four studies assess the efficacy of solitary opioid dosages and furthermore These experiments demonstrate that when compared to a placebo, opioids dramatically reduce pain. Opioids are a less common therapeutic option for rheumatoid arthritis because there isn't much data to support their efficacy in this regard[19].

Second -Line Management: Disease- modifying Anti-Rheumatoid Drugs

Reduce or halt the growth of joint deterioration to encourage remission. Slow-acting medication is defined as something which takes weeks or months to start functioning. A lengthy period of time passes before the effects of DMARDs become apparent.The risk of developing lymphoma, a condition linked to RA, can also be reduced by using disease-modifying antirhumatic drugs, or DMARDs.

The DMARDs

These medications, commonly referred to as slow-acting anti-rheumatic medicines or SAARDs, are those that alter how the illness advances. Both of the DMARD kinds are categorized. Small molecules make up Non-biological Conventional Synthetic (CS DMARDS). Sulfasalazine, hydroxychloroquine, chloroquine, leflunomide, and tofacitinib are examples of immunomodulators, while methylxate, azathioprine, and cyclosporine are immunosuppresants. The most effective RA therapy currently available is DMARDs. a 17-week research carried out in Dutch that started DMARDs right away. DMARD methotrexate (MTX) medication over an extended period of time, which reduced death by 60% compared to MTX-free patients.

Non-Biological DMARDs

It is the category of medications that are created in labs or with the use of chemicals. This covers a range of medications, including HCQ, Gold Salt, sulfasalazine, leflunomide, and methotrexate. Methotrexate, an analogue of folic acid that functions as an anchor medication or first-line therapy, totally prevents the enzymes that bind dyhydrofolic acid from converting FH-2 to folinicacid (FH-4). Supplemental folic acid can lessen the side effects of MTX. Depending on the circumstances, the medication may be given in different dosages. Thus, for the illness, this is the most recommended drug. However, because it reduces pro-inflammatory cytokines produced by monocyte generation, the antimalarial drug HCQ can be used to treat RA over an extended length of time. It also has adverse affects on the skin, GI system, etc. Although the mechanism of action of azolfidine is uncertain, sulfasalazine is utilized in combination dosages with other DMARDs. This medication is not recommended for patients who have sulfa allergies, and it is generally less taken.

Biological DMARDs

Recombinant proteins or monoclonal antibodies derived from living things are these. They are considered to be a particular kind of care. Nevertheless, it is less widely used than non-biological DMARDs because to its more severe side effects, such as increased risk of infection. The biological medications Ankianra, Abatacept, Rituximab, and TNF-Ihibitor drugs Etanercept, Infliximib, and Adalimumab are examples of these.

Surgery

When non-surgical therapies are ineffective in limiting joint deterioration, the patient is said to be in the "end stage" and needs surgical therapy. Because there are so many different treatments, the needs of each patient are considered while deciding which surgical course of action to adopt. As with knee replacements and hand tenosynovectomy, for instance.

Conclusion

- As a chronic illness, RA need therapies to alter the course of the disease. Long-term consequences may include extra-skeletal symptoms, even if the first presentations are associated with TU joint inflammation. The guidelines originate from EULAR 2016 and ACR 2015. Based on the particular location or population under study, there are distinct variations in the recommendations. The functions of baricitinib and sarilumab, as well as other exciting RA treatments, may be discussed in a future revision of the ACR recommendations.
- NSAIDs, corticosteroids, DMARDs, and opioid analgesics—which are not often used—were found to be the main medications used to treat RA. First-line treatments include NSAIDs (aspirin, naproxen), corticosteroids, and other painkillers that reduce swelling and relieve pain. These medications are prescribed to patients for symptomatic relief, while DMARDs (metoclopramide, HCQ, leflunomide, etc.) are the second line of treatment that reduces joint damage and delays or stops further joint damage. The second treatment option is a biological, which includes Rituximab and Ankianra. For the procedure, there is still one more alternative. In addition, patients benefit greatly from non-pharmacological therapy such as yoga, exercise, medicine, etc.; they must be continued or the patient must receive advice from a doctor or pharmacist. [10.12959/wjpps2016-6406] As a result, methotrexate, HCQ, and other DMARDs are typically administered and have the greatest results.

Acknowledgement

Nill

Conflict of Interest

The authors declare that there is no conflict of interest for this study

Author Contribution

All authors have contributed equally.

Informed Consent

Not required

Ethical Statement

Not required

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