Review Article

The type of infections and the use of antibiotics among patients with rheumatoid arthritis: A review

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Abstract

Patients diagnosed with rheumatoid arthritis have a heightened susceptibility to infections, which may lead to higher rates of illness and death. The heightened susceptibility may arise from the illness itself, which causes changes in the body's innate cellular defense mechanisms, or from the medications used to manage the condition. The precise level of risk for infections associated with traditional disease-modifying anti-rheumatic drugs has not been fully elucidated. This review aimed To investigate the type of infections and the use of antibiotics among patients with rheumatoid arthritis. An electronic literature search was conducted using the MEDLINE database, with the indicated search keywords: infections, antibiotics, use, patients, rheumatoid, and arthritis. To identify relevant information, the search was limited to articles published between 2017 and 2024. The researchers used suitable search terms on Google Scholar to discover and examine relevant scholarly articles. The selection of articles was determined by several inclusion criteria. The research included publications that were published from 2017 to 2024. The study was organized into many sections, each including particular categories within the analysis section.we reportrd that : Within the developing age of focused synthetic treatments for RA, severe infections persist as the primary consequence of long-term treatment. In all patients with rheumatoid arthritis, it is necessary to conduct initial screenings for hepatitis B virus and tuberculosis. Additionally, it is important to administer vaccinations for specific pathogens (such as pneumococcal, herpes zoster, and influenza) before and during treatment. Aggressive therapy should be pursued to effectively manage disease activity in RA patients, while also maintaining constant vigilance for early signs of infections. Extra care should be given to senior rheumatoid arthritis (RA) patients who are over 65 years old and have other medical conditions. These people are often more susceptible to developing infections, regardless of the medication they get. The trials conducted with different antibiotics have confirmed the effectiveness of these medications in treating rheumatoid arthritis. Thus, it is plausible that the culprit responsible for rheumatoid arthritis is a microbe, namely periodontopathic bacteria.

Keywords: Antibiotics, arthritis, infections, patients, rheumatoid, use

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory condition, with an unclear cause. Genetics, smoking, and hormones have all been linked or associated.[1]

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Recently, there has been a more thorough investigation of the concept of a microbiological trigger, which refers to illnesses of a particular body component caused by a specific pathogen. Rheumatoid arthritis development and the presence of bacteria like *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* were shown to be strongly correlated in UK research.[2] Many investigations on animals have shown a connection between the pathophysiology of inflammatory arthritis and microbiota. Models of germ-free mice do not have inflammatory arthritis. It has been shown that certain bacteria, such as segmented filamentous bacteria found in mice, cause TH17 inflammatory reactions. Joint degeneration and immune-mediated diseases may be facilitated by these interactions.[3,4]

There has been a significant rise in the number of infections in RA patients in the recent years. Specifically, there have been elevated occurrences of septic arthritis and pulmonary infections.[5] Furthermore, it is well recognized that individuals with RA have greater rates of long-term illness and death compared to the general population. The elevated mortality and morbidity in RA patients may be attributed to several factors, including an increased susceptibility to infections.[6]

Numerous bacterial diseases, including respiratory, gastrointestinal, and urinary tract infections, are widely treated with antibiotics.[7] Antibiotics that specifically target bacterial infections also disrupt the gut microbiome. These factors have a crucial role in regulating the metabolism and immune response of the host. Significantly, the microbiota may be affected by several causes, with antibiotic therapy being considered one of the most important.[8]

Antibiotic medication may cause a reduction in the quantity and diversity of microorganisms in the skin, oral cavity, and gut, which will immediately lower the number of microbes and species diversity. Antibiotic usage may increase the risk of autoimmune diseases, including autoimmune liver disease, juvenile idiopathic arthritis, inflammatory bowel diseases, and type 1 diabetes, according to several studies.[9,10] Studies have shown that antibiotics have a major impact on the composition of the gut and urine microbiome. Studies have shown that these drugs may significantly alter the gut's microbial community, with effects that last for up to a year after at least a week of therapy.[11] The use of antibiotics has been shown to disturb the microbiome; however, this association has not been fully investigated, according to new studies.

Aim of work

To investigate the type of infections and the use of antibiotics among patients with rheumatoid arthritis.

Methods

A comprehensive search was conducted on scientific websites, namely Google Scholar and Pubmed, using a variety of keywords such as Infections, Antibiotics, Use, Patients, Rheumatoid, and Arthritis, to retrieve all pertinent research publications. The chosen articles were picked based on a predefined set of selection criteria. After a thorough examination of the abstracts and notable titles of each research, we eliminated case reports, duplicate articles, and publications without complete text. The reviews analyzed in this study were published from 2017 to 2024.

Results

This analysis included research done from 2017 to 2024 on the treatment of recurrent corneal erosion syndrome. Consequently, the review was published in the discussion section under many categories, including BACTERIAL INFECTIONS, POSTOPERATIVE PROSTHETIC JOINT INFECTIONS, OPPORTUNISTIC INFECTIONS, and ANTIBIOTICS FOR RA.

Discussion

Bacterial infections

The majority of serious infections in RA patients are caused by bacterial infections.[12,13] The lung, urinary system, and skin/skin structures are the locations most often impacted. There are little disparities in the kind of isolated disease-causing microorganisms when comparing patients to the general population, except for intracellular bacteria in individuals undergoing treatment with tumor necrosis factor-α inhibitors (TNFi).[13]

Over the last 20 years, research utilizing real-world data from patient registries, randomized controlled trials, and their long-term extension studies has shown that the incidence of serious illnesses in patients with RA varies considerably, ranging from 1.5 to 7 cases per 100 patient-years.[14]

Several factors, including patient, condition, and treatment-related characteristics, have been recognized as potential risk factors for the occurrence of severe infections. Advanced age, a history of severe infection, decreased physical function, certain underlying medical conditions (especially chronic lung or renal illness), a high daily dose of glucocorticoids (above 7.5 mg/day), and a history of unsatisfactory biologic or nonbiologic treatment are among these risk factors.[13] High disease activity and a history of previous infections are the main risk factors for developing RA in patients.[15]

Postoperative prosthetic joint infections

The recent progress in the treatment of RA patients has resulted in a reduction in the frequency of arthroplasty procedures done on these individuals.[16] Prosthetic joint infection (PJI) is a severe and challenging consequence of joint arthroplasties that is difficult to cure and has a significant negative impact on the patient's health. In comparison to osteoarthritis, patients with RA have a comparable chance of needing revision surgery. However, they have a about 60% greater risk of

developing PJI, regardless of whether they are treated with biologic disease-modifying antirheumatic drugs (bDMARDs) or non-bDMARDs.[17]

A retrospective analysis of a cohort of RA patients found that the risk of severe infection within 30 days and the risk of PJI within 1 year following total knee or hip replacement surgery were comparable across various bDMARDs. On the other hand, using prednisone dosages of more than 10 mg per day was shown to increase the incidence of both severe infections and PJI. This highlights the need to gradually reduce the dosage of glucocorticoids before surgery.[17] Surgeons have recently released guidelines about the optimal time for stopping therapy in patients with rheumatic conditions who are having joint replacement surgeries. Despite being practical and user-friendly, all the advice provided is contingent.[18]

Opportunistic infections

Herpes zoster

The lifetime risk of herpes zoster (HZ), a common viral infection in the elderly population, ranges from 10% to 50%. The chance of acquiring HZ is about twice as high for those with RA diagnoses as it is for the general population. Primary risk variables include advanced age and the use of immunosuppressive medications.[19] Several studies have demonstrated that bDMARDs have not been found to significantly raise the occurrence of HZ in individuals with RA, when compared to non-biologic therapy, and no discernible differences have been seen amongst other types of biologic drugs.[20–22]

Nonetheless, JAK inhibitor-treated RA patients have a much higher risk of acquiring HZ. JAK inhibitor-treated patients had a higher incidence of HZ than the comparator group in RA, psoriasis, psoriatic arthritis, inflammatory bowel diseases, and ankylosing spondylitis patients, according to a comprehensive analysis of studies.[23] There were five filgotinib trials, six baricitinib studies, seven upadacitinib studies, and tofacitinib studies. Of the three JAK inhibitors licensed for rheumatoid arthritis, tofacitinib, baricitinib, and upadacitinib, there is currently little variation in the risk of HZ.[24]

The first JAK inhibitor authorized by the FDA in 2012 and the EMA in 2017, tofacitinib, has the most extensive longitudinal evidence on the risk of herpes zoster (HZ). According to recent research, the incidence rate of HZ was around 11% of patients or 3.9 occurrences per 100 patient-years. The majority of HZ cases were determined to be non-serious and to have only affected one dermatome. In this patient cohort, it was shown that Asian ethnicity, advanced age, and concurrent GC usage were independent risk factors for HZ.[25] Since antiviral therapy was given to 90% of patients diagnosed with herpes simplex (HZ), the incidence of post-herpetic neuralgia (PHN), the most concerning side effect of HZ was very low (7.4%). Furthermore, following their first episode, more than 85% of patients continued to take tofacitinib; of these, around 9% had a second episode of herpes zoster, 96% of which was not significant.[26]

Tuberculosis

There has been a noticeable increase in tuberculosis (TB) reactivation cases among people with an underlying latent TB infection (LTBI) that went undiagnosed as a consequence of the use of TNFi in clinical settings. Although the use of tumor necrosis factor inhibitors (TNFi) is primarily associated with the reactivation of TB, reports of TB cases occurring less frequently with other bDMARDs, and targeted synthetic DMARDs have also been made. However, the widespread use of the tuberculin skin test and/or the more modern Interferon Gamma Release Assays for patient screening before beginning bDMARD treatment has led to a notable 80% decrease in newly discovered cases of tuberculosis.[27,28]

Currently, it is believed that LTBI affects around 25% of the global population, with a frequency of 16% in the Eastern Mediterranean basin. A recent study reported a comparable frequency of LTBI among individuals with RA, ranging from 13% to 15%. IGRAs are preferred over TST for screening individuals in the general population for LTBI, because of their superior specificity and user-friendly nature. Nevertheless, for patients with rheumatoid arthritis initiating b- or ts-DMARDs, there have been suggestions to use TST, IGRA, or a combination of both for screening purposes.[29]

Hepatitis B virus reactivation

The Hepatitis B virus (HBV) continues to be the prevailing chronic viral illness on a global scale. The overall frequency of this condition has been estimated to be 3.6%, and a recent research called the International COMORA study found a comparable prevalence of 3% among individuals with RA.[30]

Like TB, a sizable portion of chronic HBV infection (HBsAg+) patients who did not get appropriate antiviral prophylaxis were at high risk of reactivation once TNFi was introduced into clinical practice. HBV reactivation may result in severe consequences such as acute hepatitis, liver failure, and potentially fatal outcomes, particularly in cirrhotic patients. Consequently, the incidence of HBV reactivation during b-DMARD therapy was decreased by the proactive use of appropriate oral antiviral medication. There are reports of HBV reactivation with all immunosuppressive medications used to treat RA, including GCs, b-, and ts-DMARDs.[31]

At present, it is recommended that all patients with RA who are beginning treatment with disease-modifying DMARDs undergo screening for HBV infection using HBsAg, anti-HBc, and anti-HBs antibodies. This screening provides the chance to identify individuals who are susceptible to HBV, whereas vaccination should be administered to patients who test negative for HBV and are at a high risk of being exposed to HBV.[31]

Patients with persistent HBsAg+ infection should be administered the latest oral antivirals as a prophylactic measure. Individuals who have had a previous or resolved HBV infection should be

closely monitored for HBsAg, HBV DNA, and ALT levels. This is particularly important for patients who are being treated with B cell-depleting agents. If there is a reactivation of HBV, antiviral prophylaxis should be initiated.[32]

Antibiotics for RA

Sulfasalazine

Sulfasalazine (SASP) was first developed by Professors Svartz, Willsteadt, and Askelof in the 1930s in Sweden. It is a combination of 5-aminosalicylic acid and sulphapyridine. The only effective antibiotics available at the time for treating "rheumatoid polyarthritis" (RA) were sulphonamides. In 1948, Svartz and colleagues published the results of their investigation on the therapeutic advantages of SASP in the management of rheumatoid arthritis. However, even with the introduction of corticosteroids in 1949 and the growing attention towards gold and penicillamine, SASPs did not gain popularity as the primary treatment for rheumatoid arthritis until the 1980s. In the same year, McConkey *et al*. reintroduced SASPs as a therapy for RA.[33] After consumption, intestinal microorganisms in the colon transform SASP into 5-aminosalicylic acid (5-ASA) and sulphapyridine (SP). While 5-ASA is not digested, 30% of the SP and SASP molecules are, indicating that SP and SASP are the most effective compounds for treating RA. Further proof that SP is the active ingredient in SASP comes from the benefits of sulfamethoxazole in the treatment of rheumatoid arthritis. Sulfasalazine, or SASP for short, is a strong antibiotic that has shown excellent results when used to treat RA.[34] In the 1940s, sulphonamides were used to treat periodontal diseases due to their effectiveness against both gram-positive and gram-negative bacteria. SASP can lead to decreased levels of white blood cells, lymphocytes, and platelets, as well as skin reactions, hives, photosensitivity, liver damage, and reduced sperm production.[35]

Tetracyclines

Tetracyclines are a family of antibiotics that are structurally related to polycyclic naphthacenecarboxamide and are generated from Streptomyces spp. Tetracyclines act as inhibitors of protein synthesis by preventing the binding of aminoacyl-transfer ribonucleic acid (tRNA) to the messenger(m) RNA-ribosome complex. Their main method of action is to bind to the mRNA translation complex's 30S ribosomal subunit.[36]

Tetracyclines have a wide range of antimicrobial activity. With a few exceptions, they have a bacteriostatic effect on nearly all medically significant aerobic and anaerobic bacterial groups, encompassing both gram-positive and gram-negative bacteria, excluding *Pseudomonas aeruginosa* and *Proteus* spp. Four double-blind, randomized clinical trials have been published that assess the effectiveness of minocycline in treating RA.[37] Oral tetracyclines are very effective against most periodontal infections, making them a common choice for treating periodontal problems. Tetracyclines possess anti-inflammatory qualities that are often unrelated to their antibacterial effects. They can hinder specific enzymes, like collagenase, which is a host-produced enzyme responsible for breaking down collagen and is created during inflammation.[38]

There are a range of potential side effects associated with tetracyclines, including loss of appetite, vomiting, feelings of sickness, difficulty swallowing, severe sunburn, dizziness, sensitivity to light, lightheadedness, skin rashes with raised bumps, allergic reactions and hives, sores in the genital area with excessive fungal growth, a spinning sensation, a severe skin condition called Stevens-Johnson syndrome, low white blood cell count, low platelet count, destruction of red blood cells, drug-induced Systemic Lupus Erythematosus, an increase in eosinophils, and a condition resembling a brain tumor called pseudotumor cerebri.[38]

Macrolide antibiotics

Macrolides are a class of antibiotics that owe their effectiveness to the presence of a macrolide ring, a sizable cyclic lactone ring. This ring may be connected to one or more deoxy sugars, like cladinose and desosamine. The lactone rings typically contain 14, 15, or 16 members. Macrolides are part of the polyketide class—a collection of natural substances.[39]

Macrolides function as inhibitors of protein synthesis. Macrolides work by slowing the production of bacterial proteins. They do this by blocking the activity of peptidyl transferase, which is responsible for transferring the peptidyl linked to tRNA to the next amino acid. Additionally, macrolides also hinder ribosomal translocation. This information is supported by reference.[39]

Macrolide antibiotics are frequently prescribed for the treatment of bacterial infections. A study was conducted by Naniwa *et al*.[40] to evaluate the effectiveness of combining clarithromycin with methotrexate and methylprednisolone for treating active rheumatoid arthritis. The study showed that incorporating a 4-week cycle of clarithromycin successfully led to the remission of the illness.

In 2024, Giamarellos-Bourboulis *et al*.[41] researched the efficacy of clarithromycin in treating rheumatoid arthritis (RA). This research was conducted using a randomized, double-blind, placebo-controlled design. Enrollment of patients was undertaken from January 25, 2021, to April 11, 2023. A total of 278 people were randomly assigned to receive standard treatment along with either clarithromycin or placebo. Achievement of the main outcome measure was observed in 68% of patients in the clarithromycin group, while only 38% of patients in the placebo group achieved the same outcome. A notable number of treatment-related adverse events were observed in 43% of individuals in the clarithromycin group and 53% of patients in the placebo group. No significant negative incidents were reported as a result of the prescribed treatment. The use of clarithromycin in the conventional treatment improves the first clinical response and reduces the inflammatory impact of community-acquired pneumonia. The mechanism of benefit is linked to alterations in the immunological response. The results indicate that it is crucial to include clarithromycin together with β-lactams when treating

patients with community-acquired pneumonia in a hospital setting. This combination leads to prompt clinical improvement and a rapid reduction in inflammation.

The most common side effects of macrolides include nausea, drowsiness abdominal discomfort, gastrointestinal issues like diarrhea, and vomiting. Occasionally, some individuals may experience less common side effects from this treatment. These can include rashes, headaches, dizziness or motion sickness, and alterations in the sense of smell and taste, such as a lingering metallic taste while taking the medication. Although less frequent, there have also been reports of xerostomia.[42]

Levofloxacin

Levofloxacin is a powerful antibiotic that effectively targets a variety of bacteria, belonging to the fluoroquinolone medication family. Levofloxacin is effective in treating infections caused by certain types of bacteria that can be found in the mouth and can survive with or without oxygen. The mechanism of action involves inhibiting the function of DNA gyrase and topoisomerase IV—crucial enzymes responsible for DNA separation and cell division inhibition. There has been a potential impact of levofloxacin on the process of mammalian cell reproduction. Several members of this pharmacological class have shown effectiveness against both bacterial and eukaryotic topoisomerases. They present a danger to cultured mammalian cells and *in vivo* tumor models.[43]

Kato *et al.*[44] demonstrated the efficacy of levofloxacin in the treatment of RA. In this study, participants with RA who continued to be actively treated with methotrexate at a stable dose of 15–25 mg weekly for at least six months were randomized to receive either 500 mg of levofloxacin or placebo orally once daily. The patients were administered methotrexate in addition to the assigned treatment. The primary measure of effectiveness was the contrast in the number of inflamed joints and tender joints from the initial assessment to the 6-month duration. The study also evaluated secondary outcomes such as pain levels, quality of life, length of morning stiffness, erythrocyte sedimentation rate, C-reactive protein level, and assessments from both physicians and patients. Data analysis was utilized to determine the number of patients who fulfilled the ACR criteria for 20%, 50%, and 70% improvement. The group that received a combination of levofloxacin and methotrexate saw the most significant decrease in the number of joints that were swollen or sensitive. The group receiving both levofloxacin and methotrexate also had significant improvement in many of the other metrics used to evaluate the treatment's effectiveness. The administration of levofloxacin was well received without any adverse effects. No harmful effects that would restrict the dosage were seen. Levofloxacin medication dramatically reduced the signs and symptoms of RA in individuals who were already receiving methotrexate for their active RA.

Common side effects of levofloxacin may include headache, nausea, dizziness, diarrhea, constipation, and insomnia. Levofloxacin therapy can lead to some serious adverse events, such as spontaneous tendon rupture and tendonitis, irreversible peripheral neuropathy, and QT prolongation/torsades de pointes.[45]

Conclusion

Within the developing age of targeted synthetic treatments for RA, severe infections persist as the primary consequence of long-term treatment. All patients with rheumatoid arthritis require baseline screening for hepatitis B virus and tuberculosis, as well as pre- and on-treatment vaccinations for specific pathogens such as pneumococcal, herpes zoster, and influenza. Aggressive therapy should be pursued to effectively manage RA and maintain disease control. Additionally, continuous monitoring for early signs of infections is essential for all RA patients. Extra care should be given to elderly rheumatoid arthritis patients (over 65 years old) who have other medical conditions, since they are generally more susceptible to developing infections, regardless of the medication they receive. The investigations conducted with different antibiotics have confirmed the effectiveness of these medications in treating rheumatoid arthritis. Hence, it is plausible that the etiological agent responsible for RA is a microbe, namely periodontopathic bacteria.

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Conflicts of interest

There are no conflicts of interest.

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