

Disease-Modifying Antirheumatic Drugs (DMARDs) and drug interactions in dentistry

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Abstract. – OBJECTIVE: Rheumatoid arthritis is a chronic autoimmune disease. Treatment aims to reduce and improve its signs and symptoms. Hence, Disease-Modifying Antirheumatic Drugs (DMARDs) are the treatment of choice. The objective of this study was to identify potential interactions between DMARDs and the drugs most frequently prescribed in dentistry in order to avoid adverse reactions.

MATERIALS AND METHODS: This literature review sets out to define possible adverse reactions provoked by pharmacological interactions between DMARDs and the drugs commonly prescribed in dentistry. A search was conducted in PubMed by searching the names of drugs used in dentistry, “drug interactions,” “rheumatoid arthritis,” and “dentistry,” “hydroxychloroquine,” “leflunomide,” “methotrexate,” “sulfasalazine,” “adalimumab,” “anakinra,” “etanercept,” “abatacept,” “infliximab” and “rituximab”.

RESULTS: It was found that most DMARDs show potential interactions with many drugs used in dentistry, including various antibiotics, analgesics, anesthetics, antifungals, and corticosteroids.

CONCLUSIONS: It is clinically important for oral health clinicians to be aware of possible drug interactions between DMARDs and the drugs commonly prescribed in dentistry to prevent potential adverse reactions and avoid endangering the patient.

Key Words:

DMARDs, Drug interactions, Dentistry, Non-steroidal anti-inflammatories (NAIDS), Antibiotics, Antifungals, Acetaminophen.

Introduction

The term rheumatism is 2,500 years old and comes from Ancient Greek, originally meaning “a flow of current”. This name alludes to the multiple joints that it affects. Rheumatoid arthritis (RA) is an autoimmune disease of a chronic and inflammatory character, synovitis being one of its

main symptoms. Its prevalence is five out of every 1000 adults, affecting more women (aged 30-50 years) than men^{1,2}.

RA is the chronic inflammation of the synovial membrane and can advance to a point at which it destroys articular cartilage and juxta-articular bone. In addition, the patient suffers multiple organ disorders, swelling, pain, and joint rigidity. After RA first appears, progressive articular destruction advances rapidly, causing deformed joints and unalterable physical abnormalities. Appropriate diagnosis and treatment play indispensable roles in dealing with this disease. Ongoing research and developments in science and technology have achieved major advances in the remission of RA at early stages or in reducing activity in established RA¹.

Diagnosis of RA is by a set of criteria established by the American College of Rheumatology and the European League Against Rheumatism in 2010. When published, these criteria included one or two novelties, such as the non-inclusion of rheumatoid nodules, erosive changes observed radiographically, and symmetric arthritis. Diagnostic tests consist principally of determining the presence of antibodies. Rheumatoid factor is not characteristic of RA alone, while anti-citrullinated protein antibodies are more specific to RA. Around 50-80% of persons with RA present rheumatoid factor, anti-citrullinated protein antibodies, or both. Other factors are globular sedimentation rates and reactive C protein levels, whose values increase with active RA. These factors are used to monitor the case, its activity, and response to medication. It is important to perform a differential diagnosis to distinguish RA from systemic erythematosus lupus, systemic sclerosis, or psoriatic arthritis³.

Regarding the established treatments for RA, Disease-Modifying Anti-Rheumatic Drugs (DMARDs) are currently the leading treatment and the subject of this literature review.

DMARDs are a set of drugs that interfere in the signs and symptoms of RA, delaying or detaining the alterations suffered by the joints. DMARDs are classified as biological or synthetic depending on provenance but can also be classified according to their route of administration, as synthetic DMARDs are administered orally, while biological DMARDs are administered intradermally or intravenously^{1,4,5}. Treatment with non-steroidal anti-inflammatories (NSAIDs) or analgesics only allows an improvement of the symptoms but does not halt the advance of the disease or the damage it causes, so these may be used as additional treatment of the symptoms or while diagnosis is being established.

This systematic literature review aimed to identify potential interactions between DMARDs and the drugs most commonly used in dentistry; it also aims to establish preventative measures to avoid adverse reactions derived from these drug interactions.

Materials and Methods

An electronic search was conducted in the PubMed and MEDLINE databases for articles reporting potential pharmacological interactions between the drugs used to treat rheumatoid arthritis (DMARDs) and the drugs most commonly prescribed in dentistry. The following search terms were applied alone or in combination: drug interactions, dentistry, rheumatoid arthritis,

hydroxychloroquine, leflunomide, methotrexate, sulfasalazine, adalimumab, anakinra, etanercept, abatacept, infliximab, and rituximab. As the articles found were few or non-existent (depending on the drug searched for), manual searches were done in official websites: Drug Interactions Checker (https://www.drugs.com/drug_interactions.html) and the National Center for Biotechnology Information (<https://www.ncbi.nlm.nih.gov>).

Results

Table I shows the number of known potential drug interactions with DMARDs of clinical significance. These drug combinations should not be administered as the risk of the interaction outweighs the benefits. They include potential interactions regarded as major, moderate or minor between DMARDs and the drugs most commonly prescribed in dentistry identified in the searches (Table II), which are as follows.

Hydroxychloroquine

Major interactions have been described between hydroxychloroquine and antibiotics belonging to the macrolide group (azithromycin, clarithromycin, and erythromycin), antifungals (fluconazole and ketoconazole), and one analgesic (tramadol). Hydroxychloroquine administered at the same time as azithromycin, clarithromycin, erythromycin, fluconazole, and ketoconazole can lead to secondary effects, such as increased and/

Table I. Number of potential drug interactions of each DMARD.

DMARDs	Number of major interactions	Number of moderate interactions	Number of minor interactions	Number of drug interactions in dentistry
Hydroxychloroquine	179	247	4	9
Leflunomide	451	90	7	11
Methotrexate	121	457	16	24
Sulfasalazine	41	159	7	7
Adalimumab	228	152	7	5
Anakinra	34	302	7	3
Etanercept	228	152	7	4
Abatacept	33	67	7	0
Infliximab	231	163	7	4
Rituximab	36	83	7	0
Tofacitinib	269	205	8	13
Baricitinib	239	107	6	9
Golimumab	228	152	7	5
Certolizumab	228	153	7	3
Tocilizumab	40	218	7	2
Sarilumab	41	159	7	1

Table II. Potential interactions regarded as major or moderate between DMARDs and the drugs most commonly prescribed in dentistry.

DMARDs	Major interactions	Moderate interactions
Hydroxychloroquine	Azithromycin, Clarithromycin Erythromycin, Fluconazole Ketoconazole, Tramadol	Carbamazepine, Itraconazole Metronidazole
Leflunomide	Acetaminophen, Acetylsalicylic acid Azithromycin, Clarithromycin, Erythromycin Carbamazepine, Clotrimazole, Fluconazole Ketoconazole, Methylprednisolone	Metronidazole
Methotrexate	Amoxicillin, Penicillin G, Penicilin V, Diclofenac, Ibuprofen, Ketoprofen, Ketorolac, Naproxen, Nitrous oxide, Omeprazole	Acetaminophen, Azithromycin Carbamazepine, Clarithromycin Clotrimazole, Cortisone, Erythromycin, Ethanol, Fluconazole Hydrocortisone, Itraconazole Ketoconazole, Tetracyclines
Sulfasalazine	Prilocaine	Acyclovir, Diclofenac, Ibuprofen, Ketoprofen, Ketorolac Naproxen
Adalimumab	Cortisone, Hydrocortisone, Methylprednisolone	Carbamazepine, Metronidazole
Anakinra		Carbamazepine, Hydrocortisone Methylprednisolone
Etanercept	Cortisone, Hydrocortisone	Carbamazepine, Metronidazole
Abatacept		
Infliximab	Cortisone, Hydrocortisone	Carbamazepine, Metronidazole
Rituximab		
Tofacitinib	Carbamazepine, Clarithromycin, Cortisone Hydrocortisone, Fluconazole, Itraconazole Ketoconazole	Diclofenac, Erythromycin Ibuprofen, Ketoprofen, Naproxen
Baricitinib	Cortisone, Hydrocortisone, Methylprednisolone	Acetylsalicylic acid, Diclofenac, Ibuprofen Ketoprofen, Naproxen Tramadol
Golimumab	Cortisone, Hydrocortisone	Carbamazepine, Metronidazole Midazolam
Certolizumab	Cortisone, Hydrocortisone	Metronidazole
Tocilizumab		Metronidazole, Carbamazepine
Sarilumab		Carbamazepine

or irregular heartbeat, which can lead to serious problems and even fatality. Patients presenting congenital long QT syndrome, conduction disorders, some heart diseases, or electrolyte disorders may be more susceptible to these adverse effects. If the patient has a history of convulsions, is in a period of abstinence from drug or alcohol consumption, is elderly, or has some effect on the central nervous system, the interaction between hydroxychloroquine and tramadol can occasionally cause convulsions. It is advisable for the patient to avoid activities that require mental agility until it becomes clear how he/she will react to these drugs⁶.

As for moderate interactions between hydroxychloroquine and the drugs used in dentistry, adverse reactions can occur with carbamazepine, itraconazole, and metronidazole. While carbamazepine can boost the level and effects of hydroxychloroquine, itraconazole reduces them. Moreover, if the patient is in treatment for epilepsy, the interaction with carbamazepine administered in dentistry to treat trigeminal neuralgia may cause a reduction in the efficacy of treatment. The interaction with metronidazole can increase the risk of nerve damage. If the patient presents weakness, pain, numbness, burning or a tingling sensation at the extremities, he/she should see the doctor⁶.

Leflunomide

Leflunomide is the DMARD that shows the highest number of interactions with the drugs commonly prescribed in dentistry: analgesics (acetaminophen, acetylsalicylic acid), antibiotics (azithromycin, clarithromycin, erythromycin), anticonvulsants such as carbamazepine (used to treat trigeminal neuralgia), antifungals (clotrimazole, fluconazole, ketoconazole) and corticosteroids such as methylprednisolone⁷. Leflunomide can provoke hepatic damage or problems and administer it with other drugs that affect the liver and increase the risk of hepatic disorders. Depending on the dose administered, leflunomide may remain in the blood for some time, so reactions may occur even though the administration has come to an end. It is advisable for the patient to avoid or minimize alcohol consumption during treatment⁷. The signs and symptoms of hepatic damage that may appear are fever, shivering, pain or swelling in the joints, bleeding or unusual bruising, cutaneous eruptions, itching, loss of appetite, fatigue, nausea, vomiting, abdominal pain, dark colored urine, light colored feces and/or yellowish skin and eyes⁷.

The use of methylprednisolone together with leflunomide can cause severe infections. Moreover, leflunomide has more interaction with alcohol, which may cause secondary effects such as reddening, head and neck palpitations, throbbing headache, difficulty breathing, nausea, vomiting, sweating, thirst, pains in the chest, increased heartbeat, palpitations, low blood pressure, dizziness, blurred vision, and confusion.

Leflunomide has a moderate interaction with metronidazole, which can cause nerve damage, this being an important secondary effect. Patients with high arterial blood pressure must be monitored during dental treatment as metronidazole alone raises blood pressure⁷.

Methotrexate

This drug has interactions with antibiotics (amoxicillin and penicillin G/V), NSAIDs (diclofenac, ibuprofen, ketoprofen, ketorolac, and naproxen), anesthetics (such as nitrous oxide) or proton pump inhibitors (such as omeprazole). When amoxicillin or penicillin are prescribed for severe infections, they are usually administered in high doses, which will provoke an interaction with methotrexate. The appearance or increase in secondary effects such as nausea, vomiting, or oral ulcers promote the onset of

anemia, infection, or blood disorders. It is necessary to adjust the dose if the patient suffers fatigue, dizziness, fainting, unusual bleeding episodes, fever, shivering or other flu symptoms. Interaction with NSAIDs will boost their effects. It is recommended to supervise the doses of both drugs whenever the patient presents ulcers or sores, mucositis, pain or swelling of the joints, yellowish skin color, dark urine, dizziness or fainting, bruising or unusual bleeding, convulsions, infection, and flu-like symptoms. Special care must be taken whenever the patient presents any renal disease⁸.

Methotrexate can have moderate interactions with various antifungals, analgesics, corticosteroids, and antibiotics. Interactions may occur with acetaminophen, azithromycin, carbamazepine, clarithromycin, clotrimazole, corticotropin, cortisone, erythromycin, fluconazole, hydrocortisone, itraconazole, ketoconazole, or tetracyclines. Taking any of these drugs together with methotrexate can affect the liver. If the patient presents signs and/or symptoms of hepatic damage, he/she should be referred to a doctor⁸. Interactions with corticosteroids are different and increase levels in the blood, causing a decrease in blood cell counts, bruising and easy bleeding, unusual feelings of weakness, mouth ulcers, nausea, vomiting, black feces or blood in feces, urinating with less frequency than usual, or not urinating at all. The same occurs with tetracyclines, but blood levels can increase or decrease, as can the secondary effects. Methotrexate also has a moderate interaction with ethanol causing hepatic problems, and so alcohol consumption should be reduced or minimized^{8,9}.

Sulfasalazine

Sulfasalazine presents interactions with the local anesthetic prilocaine. Signs and symptoms may occur within hours of administering prilocaine. The patient should seek medical attention if he/she presents grayish discoloration of the skin, mouth or nail beds, nausea, headache, dizziness, fatigue, difficulty breathing, rapid or shallow breathing, rapid heartbeat, palpitations, anxiety or confusion¹⁰.

All sulfasalazine's moderate interactions occur in combination with NSAIDs: diclofenac, ibuprofen, ketoprofen, ketorolac, and naproxen. These interactions affect mainly the renal system causing nausea, vomiting, loss of appetite, increased or decreased miction, sudden weight increase or decrease, retention of liquids, swelling, difficul-

ty breathing, muscle cramps, fatigue, dizziness, confusion, and irregular heartbeat. Sulfasalazine also interacts with acyclovir with similar effects to NSAIDs¹⁰.

Adalimumab

This is a drug of biological origin that interacts with corticosteroids: cortisone, hydrocortisone, and methylprednisolone. Interactions with these drugs can cause severe infections, with even a risk of fatality. If the patient presents any signs or symptoms of the following and is taking both types of medication, he/she should seek emergency medical attention at once: fever, shivering, diarrhea, sore throat, muscle pain, difficulty breathing, blood in the phlegm, weight loss, red or inflamed skin, body sores, pain or a burning sensation when urinating¹¹.

Moderate interactions take place with carbamazepine and metronidazole. Interaction with carbamazepine can reduce the levels and effects of the adalimumab. In combination with metronidazole, there is a risk of nerve damage¹¹.

Etanercept

Etanercept can interact with cortisone and hydrocortisone, leading to potentially major infections, with the usual signs and symptoms: fever, diarrhea, muscle pain, and weight loss, among others¹².

Moderate interactions with etanercept are the same as those between adalimumab and carbamazepine, and it is advisable to adjust the dose carefully. The same occurs with metronidazole. The patient should seek medical attention if he/she presents weakness, numbing, pain, burning or tingling in the extremities as these could be signs and symptoms of nervous damage¹².

Infliximab

Infliximab can produce interactions in combination with corticosteroids, cortisone, and hydrocortisone, increasing the risk of severe infection, which may be lethal if not dealt with in time. The signs and symptoms are the same as those cited above for interactions with adalimumab. As for moderate interactions, these are the same as with adalimumab and etanercept with the same signs, symptoms and recommendations¹³.

Tofacitinib

RA patients treated with tofacitinib can suffer problematic interactions when it is administered in combination with anticonvulsants such as car-

bamazepine, antibiotics (clarithromycin), corticosteroids (corticotropin, cortisone, hydrocortisone) or antifungals (fluconazole, itraconazole, ketoconazole)¹⁴.

Carbamazepine can reduce the effects of the tofacitinib, while clarithromycin, itraconazole (used to treat fungal throat infection), fluconazole, and ketoconazole increase them, with the appearance of secondary effects (low blood cell counts, anemia, severe infections, and high blood lipid levels)¹⁴. With cortisone, hydrocortisone and methylprednisolone, there is a possibility of severe infection, and patients may suffer additional adverse effects such as diverticular disease, bleeding or gastrointestinal perforation. The signs and symptoms that these complications present are abdominal pain, fever, vomiting or nausea.

As for moderate interactions with tofacitinib, care should be taken whenever the following are administered: diclofenac, ibuprofen, ketoprofen, or naproxen. These produce adverse effects in the gastric system, producing intense abdominal pain, fever, nausea or vomiting. Lastly, the antibiotic erythromycin can eliminate the effects of tofacitinib¹⁴.

Baricitinib

Baricitinib can interact with the following corticosteroids prescribed as a part of dental treatment: cortisone, hydrocortisone, and methylprednisolone. These interactions provoke severe infections, which may even be lethal. In some cases of cortisone, hydrocortisone, and methylprednisolone administration, interactions with baricitinib can produce additional adverse effects with risks of diverticular disease or gastrointestinal perforation¹⁵.

Moderate interactions can occur with NSAIDs (acetylsalicylic acid, diclofenac, ibuprofen, ketoprofen, naproxen) and tramadol, producing adverse gastrointestinal effects that increase the risk of diverticular disease, bleeding or gastrointestinal perforation¹⁵.

Golimumab and Certolizumab

Golimumab and certolizumab interact in the same way with certain groups of corticosteroids³: cortisone and hydrocortisone. These interactions can cause severe infections, and patients must seek medical attention if any signs or symptoms appear.

Regarding moderate interactions, these can occur with golimumab in combination with carbamazepine, metronidazole, and midazolam. With

carbamazepine and midazolam, the effects of the drugs will be reduced, but with metronidazole, the interaction increases the possibility of nervous damage^{16,17}.

Metronidazole can produce a moderate interaction with certolizumab affecting the nervous system. In this case, the dose should be adjusted or compatible alternatives prescribed. If the patient presents weakness, numbness, burning or tingling sensations in the extremities, he/she should seek medical attention^{16,17}.

Anakinra

Anakinra can have moderate interactions with corticosteroids, hydrocortisone and methylprednisolone, increasing the risk of severe infection. If the patient presents signs and symptoms of infection as described above, he/she should seek medical attention. Anakinra can also interact with carbamazepine, reducing the effects of both drugs¹⁸.

Tocilizumab

Moderate interactions may be produced by tocilizumab in combination with carbamazepine, leading to a reduction in carbamazepine levels. Monitoring and adjustment of the dose are recommended, particularly when tocilizumab administration is suspended. This drug also interacts with metronidazole, affecting the nervous system¹⁹.

Sarilumab

A moderate interaction can be produced when sarilumab and carbamazepine are administered simultaneously, reducing the effects of the latter²⁰.

Regarding slight pharmacological interactions between DMARDs and the drugs used in dentistry, none have been reported. There is also a group of DMARDs that have been found not to interact with the drugs commonly used in dentistry, although they interact with drugs prescribed in other medical fields. These are abatacept and rituximab, both of biological origin¹.

Discussion

When RA is diagnosed, basic treatment consists of assessing the situation at once before articular destruction occurs to avoid arthritis and halt the advance of the disease. The standard treatment is to prescribe methotrexate (a con-

ventional synthetic DMARD), which is not the DMARD that presents the most interactions with drugs used in dentistry^{1,4,5}. Nevertheless, the interactions that do exist are serious and so special care must be taken whenever it is administered. Adverse reactions deriving from drug interactions with methotrexate usually provoke hepatic and gastrointestinal dysfunction. If the reactions are not resolved by one of the various alternatives such as vitamin B9 administration or adjusting the dose, medication will have to be terminated in the following order: glucocorticoids, anti-inflammatories, and lastly DMARDs¹.

The present review was conducted in response to the uncertainties that arise in routine dental clinical practice whenever a patient is diagnosed with RA and seeks dental treatment²¹⁻²⁵. Information about pharmacological interactions between DMARDs and drugs used in dentistry is fairly scarce. DMARDs are immunosuppressants and so patients taking this medication and attending the dental clinic for some treatment involving other drugs already suffer a higher risk of bleeding and infection. In this sense, it is advisable to look into the patient's complete medical history to identify any renal or hepatic pathologies the patient may have presented, especially when the treatment for RA consists of drugs belonging to the DMARD group. If the RA patient attending the dental clinic requires some analgesic, we should always ask whether he/she is taking corticosteroids or mononuclear antibodies in order to revise the dose and avoid overdosing.

It is a known fact that methotrexate has adverse effects on liver function and provokes the appearance of mouth ulcers^{8,23}. It is contraindicated for patients with any renal insufficiency or patients with hepatitis C. Leflunomide also has adverse hepatic and gastrointestinal effects⁷. It is advisable to consider prescribing azithromycin in combination with these two DMARDs (leflunomide/methotrexate), or failing this, to adjust methotrexate or leflunomide doses carefully³.

When hydroxychloroquine or sulfasalazine are being prescribed, the dentist must pay special attention to the gastrointestinal system. With biological DMARDs (adalimumab, certolizumab, etanercept, golimumab and infliximab) patients should be screened for latent tuberculosis by means of a Mantoux test or thorax radiograph to ascertain presence or absence of the disease, as a propensity to develop TB and other opportunistic infections are among the adverse effects of this group of drugs^{11-13,17,18}.

Hydroxychloroquine

Among the possible pharmacological interactions that can occur with hydroxychloroquine, special care should be taken when administering antifungals and antibiotics, as the interaction produced can affect the heart rate, especially in patients presenting cardiac pathologies. The dentist must bear in mind the possible incidence of convulsions resulting from its interaction with tramadol. To manage moderate interactions, revising the doses of the drugs prescribed is recommended, especially when prescribing metronidazole, as there is a risk of the interaction causing nervous damage^{6,9}. Hydroxychloroquine accumulates in the liver, reaching much higher levels than in blood plasma.

Leflunomide

Drug interactions with leflunomide are numerous and relevant to dentistry. Special care must be taken to avoid the possible hepatic damage that these interactions can cause. There is also a strong possibility of severe infection when leflunomide is administered simultaneously to methylprednisolone, and patients must be monitored for any signs or symptoms. It is advisable to seek an alternative to prescribing metronidazole to avoid damage to the nervous system through its interaction with leflunomide⁷.

Leflunomide also has a potential interaction with alcohol, so the dentist must take care not to prescribe any mouthwash containing alcohol⁷.

Methotrexate

When patients are taking methotrexate, special care must be taken as this DMARD interacts with various drugs producing severe infections, mucositis, pain or swelling in the joints, yellow skin discoloration, dark urine, dizziness or fainting, bruising or unusual bleeding, or convulsions. One of the secondary effects is the appearance of mouth ulcers⁴, which is due to a lack of folic acid or overdosing; it has been noted in various clinical cases that increasing the dose to the point of overdose causes the appearance of ulcers in different parts of the oral cavity²³. Prescription of mouthwashes containing chlorhexidine and benzylamine hydrochloride at sufficient doses will resolve the ulcers completely. Folic acid supplements are also recommended²³, as it has been shown that the onset of adverse effects partly depends on factors that include a lack of folates¹. Methotrexate acts by controlling lymphocyte and synoviocyte proliferation through an antagonist

action against folic acid. For this reason, folic acid supplements are usually administered to avoid the appearance of adverse reactions. These reactions mainly affect the hepatic and gastrointestinal systems⁸.

The hepatotoxicity that can appear as a result of these interactions is due to the fact that they can reduce the excretion of methotrexate through their effect on the renal tubules²³. The same can occur with penicillin²². The mechanism of action of NSAIDs is transferred to any drugs linked to proteins and endangers renal function, increasing levels of free methotrexate, which usually attaches to 50-60% of albumin. This group of NSAIDs includes ibuprofen, ketoprofen, and naproxen. As these are often used in dentistry, their prescription must be applied with caution, or they should be replaced by other NSAIDs⁹. Due to the hepatotoxicity caused, liver enzyme (SGOT and SGPT) levels increase⁴. Moreover, methotrexate presents an interaction with nitrous oxide, and so the anesthesiologist should be consulted to assess the indication or contraindication of inhalation sedation in dental treatment.

Liver damage that may be caused by methotrexate's potential moderate interactions, which should be taken into account before prescribing it. Any appearance of the signs and symptoms of gastrointestinal damage is a clear signal that a medical check-up is necessary.

Little information is available about one possible interaction between methotrexate administered at the same time as bisphosphonates. One clinical case reports a patient who, after treatment with methotrexate, began treatment for osteonecrosis of the jaw with bisphosphonates. A wound that would not close was observed, which led to the suspension of the methotrexate, which seemed to tip the balance towards slow healing. In spite of the efficacy of this drug, its use is restricted by the secondary effects it causes²⁶.

Sulfasalazine

Special care is recommended when prescribing sulfasalazine and prilocaine as it increases the risk of methemoglobinemia, a situation that leads to reductions of oxygen in vital organs and tissues due to reduced oxygen transportation in blood. This drug also presents moderate interactions with many NSAIDs commonly used in dentistry to relieve pain. It is recommended to prescribe an alternative to these NSAIDs to avoid possible adverse reactions¹⁰.

Adalimumab

Interactions with adalimumab produce severe infection which unless managed can even lead to death. Nerve damage is likely to occur through its interaction with metronidazole, and the dentist should bear this in mind whenever prescribing adalimumab¹¹.

Etanercept

Adverse effects can occur with etanercept's interactions with cortisone and hydrocortisone, including a propensity to potentially severe infection. In addition, there is a risk of nerve damage through its interaction with metronidazole. Doses should be revised if treatment with carbamazepine begins, as there is also a risk of interaction¹².

Infliximab

The potential moderate interactions and adverse effects that infliximab can cause are the same as with adalimumab, both belonging to the same family of medicines². The drug acts against tumor necrosis factor (TNF) and is now used to treat more than ten immunological diseases, including Kawasaki disease, psoriasis, Crohn's disease, and ulcerative colitis. Therefore, these systemic diseases must be identified in the patient's medical history to assess the risk of drug interactions in dental treatment¹³.

Tofacitinib

Interactions with tofacitinib take the form of increases or decreases in the drugs levels and effects. This is very important due to the fact that an increase can lead to overdose and secondary effects, while a decrease will interrupt the desirable effects of the drug in managing RA. This happens when it is administered together with anticonvulsants such as carbamazepine, which reduces tofacitinib levels. But the antibiotic clarithromycin and antifungals fluconazole, itraconazole, and ketoconazole increase them. There is also a possibility of major infection through other interactions. Special care should be taken when prescribing NSAIDs as they have moderate interactions with tofacitinib, adversely affecting the gastrointestinal system¹⁴.

Baricitinib

The corticosteroids used in dentistry can interact with baricitinib, provoking severe infection. Interactions can also damage bone marrow, the immune system or even cause diseases of the colon or gastrointestinal perforations. Special care

should be taken regarding the latter, as NSAIDs aspirin and tramadol also have adverse effects on the digestive system¹⁵.

Golimumab and Certolizumab

Like other drugs used to treat RA, interactions with golimumab and certolizumab can cause major infections that are potentially lethal. It is recommended to avoid prescribing metronidazole with either of these drugs, as moderate interactions can cause damage to the nervous system^{16,17}.

Anakinra

The patient should be warned that infection can occur and if any signs or symptoms appear, he/she should seek medical attention¹⁸.

Tocilizumab

Damage to the nervous system can occur when tocilizumab is taken simultaneously with metronidazole, and so an alternative should be prescribed in dental treatment¹⁹.

Sarilumab

A possible interaction with carbamazepine can reduce the effects of sarilumab²⁰.

Conclusions

In summary, secondary effects, ranging from slight to severe, can occur due to interactions between the drugs prescribed in dentistry and those prescribed to treat RA. Dentists need to be aware of these interactions to prevent the appearance of possible adverse reactions that endanger the patient.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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