PALLIATIVE PEARLS
BY ENCLARA PHARMACIA

Symptom Management of Rheumatoid Arthritis
September 2019

PATIENT CASE

RJ is a 60 y/o male admitted to hospice with a primary diagnosis of Hodgkin lymphoma. Co-morbid conditions include COPD, hyperlipidemia, hypertension and rheumatoid arthritis. He has no drug allergies and lives at home with his partner.

Rheumatoid arthritis was diagnosed 6 years ago, and RJ responded well to the combination of oral methotrexate and subcutaneous etanercept (Enbrel®). When RJ was diagnosed with lymphoma, both medications were discontinued while he underwent palliative chemotherapy. In a short time, RJ experienced an exacerbation of his rheumatoid arthritis (painful and swollen hands, wrists and knees) and was then initiated on naproxen 500mg, one tablet by mouth twice daily. RJ continues to take naproxen despite minimal relief. It is noted that he stopped chemotherapy shortly before electing hospice.

What options exist for management of RJ's pain and inflammation?

AUTOIMMUNE DISORDERS

More than 80 types of autoimmune disorders occur as a result of an individual's immune system attacking its own organs, tissues and cells.[1] An autoimmune disorder may affect one or more of the following organs and/or tissues, as the immune system is unable to "distinguish between healthy tissue and potentially harmful antigens": Blood vessels, connective tissues, thyroid gland, pancreas, joints, muscles, red blood cells and skin.[2] The cause of many autoimmune diseases is not known however thought to be impacted by genetics, infections and/or environmental exposures.

Autoimmune disorders can fluctuate between a state of remission, with little or no symptoms, to exacerbation, resulting in pronounced symptoms. Treatment is focused on weakening or dulling the immune system's response and thus alleviating the symptoms of inflammation. An autoimmune disorder in remission prevents the permanent joint and tissue damage that results from prolonged inflammation.[3]

Common Autoimmune Disorders:[2]

- Addison disease
- Celiac disease
- Graves disease
- Hashimoto thyroiditis
- Hashimoto's disease
- Inflammatory bowel disease
- Multiple sclerosis
- Myasthenia gravis
- Psoriasis
- Rheumatoid arthritis

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- Sjögren syndrome
- Systemic lupus erythematosus
- Type I diabetes

Common Symptoms:[3]

- Joint - Pain, swelling and stiffness
- Thyroid - fatigue, weight gain, muscle aches
- Skin problems - Redness and other color changes, rashes, blisters
- Gastrointestinal - Abdominal pain and/or digestive issues
- Recurring fever
- Swollen glands

RHEUMATOID ARTHRITIS (RA)

Rheumatoid arthritis (RA) is characterized by joint inflammation and, when left to progress, the potential to destroy both cartilage and bone. Joints of the hands, feet, wrists, elbows, knees, and ankles are most commonly affected, typically bilaterally (e.g., both hands, both knees). Systemic inflammation caused by RA may also impact other areas such as blood vessels, eyes, nerves, and the heart.[4]

Similar to other chronic conditions, management of an autoimmune disorder at end-of-life, is focused on palliation of symptoms with less importance on long-term prevention of joint and tissue damage.

Nonpharmacologic management:[5]

- Heat and cold therapies
- Orthotics and splints
- Therapeutic exercise
- Occupational therapy, with assistive devices where appropriate
- Joint-protection and energy-conservation education (good posture, avoiding overuse, modifying tasks to decrease joint stress, using appropriate splints)

Vaccinations are recommended by the American College of Rheumatology (ACR) before any pharmacotherapy targeting RA begins and include pneumococcal, hepatitis, influenza, human papillomavirus (HPV) and herpes zoster virus (HZV) vaccinations.[6]

Pharmacologic management:

Disease-modifying anti-rheumatic drugs (DMARDs) are agents that target specific cytokines or other molecules to suppress inflammatory response, primarily by downregulating the immune system.[5] They can be synthetic drugs or biologic agents and include:

- **Non-biologic DMARDs (aka. traditional DMARDs)**: Hydroxychloroquine (Plaquenil®), sulfasalazine (Azulfidine®), methotrexate (MTX), leflunomide (Arava®)

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- **Biologic DMARDs - TNF inhibitors**: Etanercept (Enbrel®), infliximab (Remicade®), adalimumab (Humira®), certolizumab (Cimzia®), golimumab (Simponi®)
- **Biologic DMARD - non-TNF agents**: Rituximab (Rituxan®), anakinra (Kineret®), abatacept (Orencia®), tocilizumab (Actemra®), sarilumab (Kevzara®), tofacitinib (Xeljanz®), baricitinib (Oluminant®), upadacitinib (Rinvoq®)

Corticosteroids are anti-inflammatory drugs commonly used to bridge the time until treatment with DMARDs is effective. They are also effective adjuncts to DMARD or NSAID therapy.[5] Corticosteroids have disease modifying effects in rheumatoid arthritis, as they retard the progression of erosions. In patients with longer prognoses, corticosteroids are reserved for exacerbations and short therapy durations to limit long-term side effects such as bone fractures, hypertension, osteoporosis and hyperglycemia.[4] Examples include prednisone, methylprednisolone (Medrol®) and dexamethasone (Decadron®).

Non-steroidal anti-inflammatory drugs (NSAIDs) interfere with prostaglandins thus reducing swelling and pain. Unlike corticosteroids, NSAIDs do not retard joint destruction and are not sufficient to treat RA when used alone. Like corticosteroids, NSAIDs use is typically temporary, as a means to bridge the time until DMARD therapy is effective.[4,5] Examples include ibuprofen (Motrin®, Advil®), naproxen (Naprosyn®, Aleve®), ketoprofen (Orudis®), piroxicam (Feldene®), diclofenac (Voltaren®) and celecoxib (Celecoxib®).

Other agents may be used to manage pain that do not affect swelling or joint destruction and include acetaminophen and opioids.

CANCER AND RA

Utilization of DMARD therapy in patients with concomitant cancer and RA requires careful consideration of the risks and benefits of therapy balanced with the cancer type and stage, patient prognosis and goals of care.

Patients with cancer concurrent with rheumatoid arthritis are at increased risk for morbidity and mortality.[7] DMARDs and corticosteroids used to treat RA can increase the risk of infection, especially in patients receiving chemotherapy. It has been proposed that the use of biologic DMARDs may increase the risk of cancer and/or cancer progression. Although patients with RA have an increased risk of certain types of cancer (e.g., lymphoma, lung cancer) already, presumably due to being in a chronic inflammatory state,[8] there is no evidence thus far that biologic DMARDs increase the risk of developing non-skin solid tumors.[9-11]

The American College of Rheumatology (ACR) provides guidance on how to manage RA in patients on previously-treated cancer, however provides no specific recommendations for patients with active cancer. General consensus has been to discontinue biologic DMARDs in patients with active cancer receiving chemotherapy.[6] In advanced disease, the treatment goals are palliative in nature, not curative, however an exacerbation of RA in the absence of DMARD therapy can significantly affect a patient's quality of life.

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PATIENT CASE ASSESSMENT

Combination therapy with oral methotrexate and etanercept injections controlled patient RJ's rheumatoid arthritis. He needed to discontinue DMARD therapy when chemotherapy was initiated. Although chemotherapy is no longer a part of RJ's plan of care, he has not restarted DMARD therapy but agreed to a trial of naproxen. Now with a short prognosis, on hospice services, an exacerbation of RA has left him considerably uncomfortable. It may be reasonable to resume RA on DMARD therapy however he will need to be presented with the potential risks (e.g., infection (including the site of injection), severe GI toxicity, blood dyscrasias, cost) and benefits, as well as alternative options (e.g., oral corticosteroid trial, opioid therapy), before adjusting his plan of care.[11]

For additional information on this topic please refer to the below references:

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