Treatment complexities in rheumatoid arthritis

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The case of Mrs A:

Mrs A is a 52-year-old woman who presented with an acute flare of her rheumatoid arthritis (RA). For the last three months, Mrs A had felt 'out of sorts'. She had an episode of being unwell with a sore throat and 'tiger scratch' lesions on her arms. In the prior few weeks, every day was a struggle. She had gone from being fully independent, to severely restricted in her activities.

Mrs A does not take any regular medications. Thirty years ago, she made a decision to avoid medications because the side effects made her feel 'rotten'. As a young person she experienced tinnitus from high-dose salicylate therapies. After stopping medications, she felt 'wonderful'. Her experiences guided her decision to self-manage her condition with dietary manipulation, exercises, and membership of support groups for the past 30 years.

Mrs A has asthma for which she takes corticosteroids. She is a mother of four. She has spent most of her life caring for her family. She is a non-smoker. She has a family history of arthritis. Her father has ankylosing spondylitis with complications of iritis. He has the human leukocyte antigen B27 (HLA B27) tissue type, which Mrs A would have a 50% chance of also having. Similarly, he self manages and does not take medications for his condition. An important challenge in Mrs A's care is re-engaging her and her whānau in medical management.

On examination Mrs A had Bouchard's and Heberden's deformities of the proximal and distal interphalangeal joints of the hands, respectively. She had swan-neck deformities of the right index finger and left ring finger. She had a Boutonniere contracture in her left, middle finger. She had a fixed, flexion deformity of both distal interphalangeal joints of the little fingers, with internal rotation at the proximal interphalangeal joints. She had marked synovitis bilaterally of the metacarpal phalangeal joints, with subluxation of the right thumb. Finally, she had synovitis of both wrists with bilateral ulnar deviation of around ten degrees of medial rotation.

Mrs A was unable to extend her fingers to 90 degrees. She was unable to make a closed fist. Functionally she was able to turn a key, do up a button, and write. Other pertinent findings on examination were synovitis of the knees with a negative patellar tap, severe pain on palpation and passive movement of the right hip, and boutonniere deformity of the right, little toe.

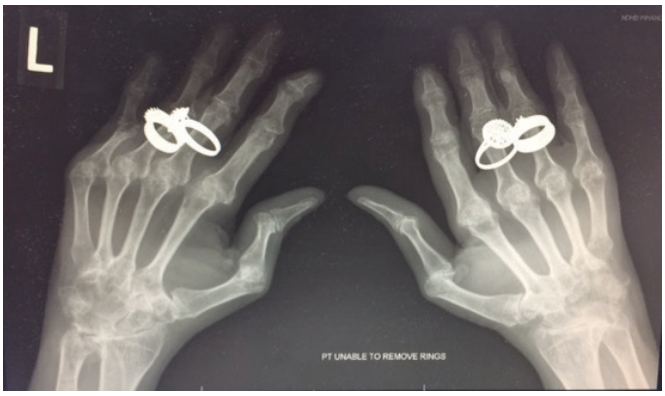

Figure 1 Plain film of left and right hands.

Investigations

1. Raised inflammatory markers: C-reactive protein 150, erythrocyte sedimentation rate 41.

2. Plain films of the hands, shoulders, elbows, pelvis, knees, and ankles were taken. There were widespread degenerative changes throughout the phalanges. Additionally, severe degenerative changes were noted in the right hip joint. Plain films of the elbows, ankles, and knees showed mild degenerative changes.

3. Rheumatoid factor 9 (reference range: 0-14).

4. Negative tests for perinuclear and cytoplasmic anti-neutrophil cytoplasmic antibodies.

5. Farr assay/negative anti-double stranded deoxyribonucleic acid antibodies (dsDNA) – used to test for systemic lupus erythematosus.

6. We did not investigate for HLA B27 tissue type.

Problem list

1. Acute flare of RA.
2. Poorly controlled RA with long-standing disability.
3. Surgical candidate for a right, total hip-joint replacement.
4. Loss of engagement with pharmacological management.
5. Potential HLA B27 tissue type.

Mrs A is a 52-year-old woman who presented with an acute flare of RA. On examination she had characteristic deformities of RA. This was particularly evident in swan neck, boutonniere's, and Heberden's deformities of her hands. Her raised inflammatory factors and findings on plain film objectively pointed towards a diagnosis of RA. Other blood tests excluded differentials of systemic lupus erythematosus and vasculitis.

Discussion

Since first being described by Augustin Jacob Landré-Beauvais in the 1800s, our understanding of RA has improved, but much is still unknown.[1] We know that RA is an autoimmune disease affecting large and small joints and causing pain, swelling, and deformity in a symmetrical fashion.[2] RA typically causes long-standing deformity during the first two years following diagnosis.[3] Current strategies in New Zealand for treating RA to reduce deformity, focus on disease-modifying antirheumatic agents (DMARDS) and biological agents.

Methotrexate is an immunosuppressive DMARD. It has an unclear mechanism of action. What we do know is that it acts on dihydrofolate reductase, increasing adenosine nucleotides, which inactivate tetrahydrofolate receptors.[4,5] In brief, this means that it reduces some forms of folic-acid production in the body. The net effect of this is a reduction in joint inflammation, which improves joint pain and swelling.[5]

Methotrexate has proven benefits for people like Mrs A who suffer from active disease. Methotrexate monotherapy, when compared to placebo, showed a 15% absolute improvement (95% confidence interval 8% to 23%) in American College of Rheumatology scores for the study participants.[6] These scores focus on joint pain and swelling, and other features of active disease.[7]

Objectively, participants taking methotrexate as a monotherapy had lower rates of radiographic progression on plain film. Researchers demonstrated that 31% of patients were less likely to develop new joint erosions 52 weeks after commencing therapy, compared to those taking a placebo.[6] Overall, methotrexate by itself has both subjective and objective benefits for Mrs A and other patients with RA.

Within New Zealand, methotrexate is the dominant initial treatment for RA. Biological agents are usually available after a trial of methotrexate.[11] Biological agents decrease inflammation and joint damage by blocking pro-inflammatory molecules, which are otherwise known as tumour necrosis factors. Our decisions to fund these treatments are based on the literature, much of which has originated in America. Within New Zealand, both adalimumab (brand name Humira) and etanercept (brand name Enbrel) are funded by PHARMAC.[11]

Both adalimumab and etanercept are efficacious in the management of RA. When used in combination with methotrexate, adalimumab successfully slowed the degeneration of participants' joints with less erosions on plain films taken 52 weeks after initiating therapy.[12] Etanercept in combination with methotrexate improves pain and functioning, and reduces disease activity.[13] There was a 38% absolute improvement in the study population of patients taking etanercept and methotrexate compared to patients taking methotrexate alone.[13] For Mrs A, these treatments can assist with prevention of acute flairs, as well as further deformity and disability. Biologics have shown great promise in improving the journey of RA for patients. However, little is known about the long-term effects. This is a challenge in a population with confirmation biases towards treatment risks.

Adverse effects and side effects were cited by Mrs A as reasons for not taking methotrexate in the past. Fewer than 10% of patients experience gastrointestinal side effects such as nausea, vomiting, and abdominal pain.[5] Less commonly, and usually related to dose, patients can experience alopecia, pneumonitis, bone marrow suppression, and hepatitis with alcohol use.[8] An increased risk of lymphoma has been suggested but not yet proven in patients on methotrexate for longer than 25 years.[9] For childbearing women, methotrexate has a teratogenic effect and is not recommended during breast feeding.[8]

Some side effects from methotrexate can be alleviated with co-administration of folic acid. Folic acid has been shown to reduce gastrointestinal side effects with an absolute risk reduction of nine per 100 people.[10] Folic acid has no impact on the efficacy of methotrexate. Patients on a combined schedule were less likely to discontinue methotrexate for any reason, compared to those taking methotrexate alone.[10] A combination of methotrexate every Monday and folic acid every Friday was prescribed by a consultant rheumatologist while Mrs A was an inpatient.

As a result of the experience some patients have had, methotrexate has cultivated a negative reputation of having adverse effects.[17] Additionally, many people in our communities living with RA are unaware that folic acid has a protective effect and has been shown to reduce the risk of these side effects.[10] People are guided by what they know. In this respect, patients may focus on the negative past experiences of themselves, friends, and whānau. Medicine, and its documented use of trial and error, has not assisted with this. Mrs A has had her trust in medicine eroded by a pattern of therapies where well-meaning doctors treated her with medications that made her feel 'rotten'.

Addressing the loss of engagement in pharmacological management is a crucial issue for this whānau. A family meeting should be organised where Mrs A, her father, and other family members can raise and address their concerns with a consultant rheumatologist. We need to rebuild Mrs A's trust in medicine so that she can re-engage and we can move forward. Once we have rebuilt a therapeutic relationship, we can begin to address other issues such as the right total hip joint replacement that Mrs A may need and screening for HLA B27 to exclude an associated spondyloarthropathy that may impact management.

Patients can choose between conventional and alternative non-pharmacological management. Conventional non-pharmacological therapies include physiotherapy and occupational therapy.[16] Occupational therapy includes educational interventions, splints, assistive devices, and counselling. Occupational therapy has a proven positive effect on functional ability in patients. As part of our care plan we facilitated a referral to hand physiotherapy and provided splints for Mrs A.

Alternative therapies include dietary manipulation,[14] which includes vegetarian, elimination, and Mediterranean diets, and thermotherapy.[15] Dietary manipulation has limited evidence. While this strategy worked for Mrs A, a lack of evidence prevented us from differentiating between efficacy of this intervention and the placebo effect.[14] Similarly, patients may find some short-term benefits from thermotherapy, but both therapies lack research and proof of efficacy.

In brief, the decisions that patients make occur within the contexts of their lives. Mrs A has an in-depth historical perspective on RA from her

own experiences. She has experienced side effects and adverse effects through a range of pharmacological treatments. As a result of this, she has chosen to focus on what she can do non-pharmacologically for herself. The challenge lies in rebuilding a therapeutic relationship that enables Mrs A and her family to re-engage and rebuild trust in medicine again. We need to work with Mrs A to promote her quality of life and ensure she has every option available to best manage her RA.

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