ISSN 1391-0736

The Sri Lanka Prescriber

September-December 2022; Volume 30, No. 3 & 4

CONTENTS

Current recommendations on the management of Rheumatoid Arthritis: Frequently asked questions	**1**
Self-assessment questions	**8**
Erectile dysfunction: causes, assessment and management options	**10**

The Sri Lanka Prescriber *is sponsored by the State Pharmaceuticals Corporation of Sri Lanka as a service to the medical profession.*

The Sri Lanka Prescriber

Copies of the Sri Lanka Prescriber and inquiries from Deputy General Manager, Marketing, and Manager Promotions and Publicity (Telephone 2338102), State Pharmaceuticals Corporation, P. O. Box 1757, 75, Sir Baron Jayathilake Mawatha, Colombo 1.

Price per copy Rs 50.00 (students Rs 25.00). Personal callers may also obtain copies from the Departments of Pharmacology at the Medical Faculties in Colombo, Galle and Sri Jayewardenepura.

Published by
Department of Pharmacology
Faculty of Medicine
271, Kynsey Road, Colombo 8, Sri Lanka.
Telephone: + 94 11 2695300 Ext 315
and
State Pharmaceuticals Corporation
75, Sir Baron Jayathilake Mawatha, Colombo 1.
Telephones + 94 11 2320356-9
Fax: + 94 11 447118
E-mail: prmanager@spc.lk
Web site: www.spc.lk

Printed by
Colombo University Press
Stanley Wijesundera Mawatha, Colombo 07, Sri Lanka
Telephone: + 94 114 596 686
E-mail: press@cmb.ac.lk

The Sri Lanka Prescriber

Current recommendations on the management of Rheumatoid Arthritis: Frequently asked questions

Rheumatoid arthritis (RA) is the commonest form of chronic inflammatory arthritis with a worldwide prevalence of approximately 1%-2%. Poorly controlled RA leads to long-term adverse outcomes, disability, reduced quality of life and increased mortality. However, unprecedented advances in the field of rheumatology over the last few decades have broadened our understanding of the disease, paving way to newer therapies. This has radically changed our approach to the management of RA resulting in significantly improved disease outcomes.

The following is a synopsis of current recommendations in the management of RA.

1. How can we diagnose RA early?

Early diagnosis of RA may not always be straight forward because "textbook features" such as symmetrical polyarthritis, subcutaneous nodules and joint erosions on X rays take time to develop, and the presentation can be very varied. Yet, an early diagnosis is imperative to prevent disease progression, joint damage and ensuing disability (1).

The diagnosis of RA is based on clinical features, radiographic images and serological markers, such as rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA), commonly tested as anti-cyclic citrullinated peptide antibody (anti-CCP)(2). Checking for both RF and Anti-CCP in patients with undifferentiated arthritis increases the diagnostic yield. Although fewer than 40% of patients with early RA are positive for RF, anti-CCP antibodies can be found in blood up to 2 to 4 years prior to the onset of clinical disease. However, it is important to bear in mind that a subset of patients with RA can remain negative for both RF and anti-CCP throughout the course of the illness. As plain X ray changes in RA appear only when the joint has already sustained some damage and the periarticular osteopenia seen in the initial phases might be subtle and missed easily, other imaging modalities such as joint ultrasound and in certain occasions magnetic resonance imaging (MRI) can be extremely useful to identify changes such as synovitis, subtle joint effusions, bone marrow oedema and erosions early (3).

American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 rheumatoid arthritis classification criteria emphasize on characteristics that emerge early in the disease course and may help identify patients with early RA (2). However, it is important to recognse that these are not diagnostic criteria, and that RA is in fact very much a clinical diagnosis.

2. When should DMARDs be initiated in patients with newly diagnosed RA?

A few decades ago, a pyramidal approach was followed to treat RA; starting with analgesics, then with non-steroidal anti-inflammatory drugs (NSAIDs) and ultimately using DMARD in patients who have persistent disease. As opposed to this, starting DMARDs early became the best practice in the 1990s. This paradigm shift was incited by evidence from large studies which showed that active inflammation and the bulk of the disease occurred in the initial phase of the RA and suppressing inflammation within this "window of opportunity" prevented disease progression, joint damage and disability (4).

We have now moved a step further. It is recommended that therapy with DMARDs should be started as soon as the diagnosis of RA is made. Now our goal is to "treat to target",

with treatment aimed at reaching a target of sustained remission or low disease activity in every patient. If at least a 50% improvement in disease activity is not observed within the first 3 months, or if the target it not reached by 6 months, therapy should be modified.

3. What is the drug of choice in treatment naïve patients?

Since the US Food and Drug Administration's (FDA) approval of methotrexate (MTX) for the treatment of RA in 1988, it has remained the initial drug of choice among rheumatologists.

All current guidelines including the 2022 EULAR recommendations (5) and 2021 American College of Rheumatology (ACR) guideline (6) recommend MTX over other conventional DMARDs (csDMARDs). Therefore, MTX remains the anchor drug of choice unless contraindicated or not tolerated.

Oral MTX is preferred over subcutaneous MTX in treatment naïve patients, particularly due to lower cost, and the dose is escalated to a weekly dose of about 0.3 mg/ kg within 4–6 weeks with sufficient folic acid supplementation. Compared to Caucasians in whom the optimal therapeutic dose is 20-25 mg per week, it is lower in Asian populations due to lower body weight and differences in pharmacogenetics (7). MTX is administered with a minimum of 5mg of folic acid per week taken on a day other than when MTX is administered. Nausea, vomiting and gastrointestinal intolerance is common and the MTX dose can be split over 24 hours, or it can be switched weekly subcutaneous injections if gastric side effects are intolerable. Increasing the dose of folic/folinic acid also helpful to minimize side effects. If these strategies fail, the patient is switched on to an alternative DMARD(s).

4. What about patient in whom MTX is contra-indicated or who have early intolerance?

Both leflunomide and sulfasalazine have been shown to improve the signs and symptoms of RA as well as retard radiographic progression. In patients with moderate-to-high disease activity with a contra-indication to MTX or early intolerance, leflunomide (LEF) or sulfasalazine (SSZ) should be considered as part of the initial treatment strategy (5, 6). However, the 2021 ACR guideline is vague about the place of SSZ possibly due to concerns over its long-term tolerability.

5. What DMARD is preferred in treatment naïve patients with low disease activity?

Hydroxychloroquine (HCQ) may be used in patients with low disease activity without poor prognostic factors, if MTX, SSZ and LEF are contra-indicated (5). In previous guidelines HCQ was preferred over other csDMARDs because of its more favorable risk profile and better tolerability in patients with low disease activity (6). However, HCQ has shown only a weak clinical benefit and no efficacy in preventing structural joint damage in general and historic studies (8). SSZ may also be considered over MTX or LEF because it is less immunosuppressive.

6. Is combination therapy preferred over monotherapy in treatment naïve patients with moderate-to-high disease activity?

This is an issue that has been extensively debated and investigated over the years. A few randomized control trials have shown dual or triple therapy to be more efficacious than monotherapy (of either MTX or SSZ) but consistently associated with higher risk of hepatotoxicity. Considering the higher burden of combination therapy with multiple medication and increased cost as well as increased risk of adverse effects, the 2021 ACR and the 2022 EULAR guidelines recommend MTX monotherapy over combination therapy in treatment naïve patients (5, 6). However, some rheumatologists opt for combination therapy

with close monitoring for toxicities based on their personal preference and patient factors. Of course, considering the cost of biologics and targeted synthetic DMARDs (tsDMARDs), combination therapy of csDMARDs remains a reasonable option for patients who fail to achieve treatment targets on monotherapy, particular in resource limited settings as Sri Lanka.

7. Is there a place for glucocorticoids?

Glucocorticoids are used as a bridging therapy to alleviate symptoms prior to the onset of action of DMARDs. While it is not routinely used across the board, it can be particularly useful in patients with moderate-to-high disease activity who are debilitated by their symptoms (9). It is limited to the lowest effective dose for the shortest duration possible, starting with a dose that is tailored for each patient. If there is a failure to sustain the treatment target on tapering or withdrawal of glucocorticoids, it should be regarded as failure of the initial therapeutic strategy and calls for an adjustment of therapy. Furthermore, intra-articular glucocorticoids are also commonly used when a single joint is flaring for quick relief of symptoms while DMARD therapy is being optimized. Some rheumatologists also offer episodic intramuscular depot injections to control flares, but it should not be the principal treatment strategy for flares.

8. What if the target is not achieved with the first csDMARD strategy?

In such cases one could either combine csDMARDs or add a biologic DMARD (bDMARD) or a targeted synthetic DMARD (tsDMARD). This choice is highly preference sensitive, depending on the setting, physicians' preferences, patients' expectation and preferences and should also take into account other patient factors such as co-morbidities and disease severity.

Randomized controlled trials have demonstrated equivalent long-term outcomes between triple therapy with csDMARDs (MTX or LEF with SSZ and HCQ) and addition bDMARD or tsDMARD. The societal cost associated with triple therapy is also significantly less than bDMARDs or tsDMARDs. Despite this, the current guidelines recommend the latter over triple therapy because patients may prefer maximizing improvement as quickly as possible and there would be greater persistence compared to triple therapy. However, in lower resource settings such as ours, triple therapy is commonly used due to limited availability and high cost of bDMARDs and tsDMARDs. Often switching to or adding on another csDMARDs in the absence of poor prognostic factors such as persistently high disease activity despite treatment, high acute phase reactant levels, high swollen joint count, presence of high RF levels and/or ACPA, and presence of early erosions is practiced. If there are no poor prognostic factors, a bDMARD should be added to initial csDMARD. tsDMARDs (JAK inhibitors) can be considered as alternative to bDMARDs, if there are no cardiovascular and malignancy risk factors. On the other hand, adding a csDMARDs is recommended over addition of a bDMARD or tsDMARD for patients who have had serious infections within the previous 12 months.

9. What bDMARD or tsDMARD is preferred for such patients?

In modern practice we are rather spoilt for choice. The choices of biologic therapies for RA include TNF inhibitors (e.g. adalimumab, certolizumab, etanercept, golimumab, infliximab) interleukin 6 receptor inhibitors (IL- 6Ri) (e.g. sarilumab, tocilizumab), T cell costimulatory inhibitor (abatacept) and anti-B cell CD-20 antibody, rituximab along with biosimilars of TNF inhibitors and rituximab. The tsDMARDs are JAK inhibitors which include baricitinib, tofacitinib, upadacitinib and figlotinib. There is no current recommendation for one bDMARD over another. Therefore, the decision is again based on physician preference, patient's preference, other patient factors and availability. However, with new evidence on

adverse cardiovascular events and malignancy risk of JAK inhibitors, bsDMARDs are preferred in such pertinent risk factors (5).

Continuing a csDMARD (e.g. MTX) along with bDMARD should be considered particularly for TNF inhibitors and presumably other therapies to increase the efficacy of the bDMARD. If a csDMARD cannot be continued, IL-6i or a tsDMARD is preferred as they generally have good clinical efficacy even as monotherapy. Furthermore, patient's co-morbidities should be considered, and an individualized decision should be made (e.g. JAK inhibitors should be avoided in patients who are at higher risk of CV events, stroke, blood clots, or malignancy including individuals older than 65 years, TNF inhibitors are contraindicated in those with NYHA class III and IV heart failure, abatacept is preferred over TNF inhibitors in patient with nontuberculous mycobacterial lung disease).

10. What if all of the above fail to achieve the treatment target?

If a patient has ongoing joint pains, it is important to determine whether it is due to active RA or due to other cause such as osteoarthritis or fibromyalgia as these could often coexist. If there is ongoing RA disease activity, compliance to therapy should be assessed and confirmed prior to escalating or adjusting treatment.

RA is a heterogenous disease and patients require access to multiple medication with different modes of action to address this heterogeneity. Patients may potentially need switching between medication (cycling) if no improvement is seen with one treatment strategy. If a patient does not achieve treatment target on a bDMARD or tsDMARD, it is recommended to switch to a bDMARD or tsDMARD of a different class over switching to one of the same class because evidence suggests there is greater improvement in disease activity and survival among patients switching classes. Although there is some emerging data that suggests presence of RF is closely associated with a good response to rituximab or abatacept when treatment with a TNF inhibitor has failed there are no well-established predictive biomarkers to predict treatment response and adjusting treatment is very much a process of trail and error.

11. What pre-treatment assessments should be done prior to starting DMARDs?

Most DMARDs carry the risk of bone marrow toxicity and liver toxicity. Therefore, nearly all patients require a full blood count, liver function tests, serum electrolytes, blood urea, serum creatinine, eGFR, and C-reactive protein at baseline. A chest X ray (if not performed within the 6 months) should be done prior to starting MTX and lung functions may be done in patients with pre-existing lung disease. All patients who are to be commenced on bDMARDs or tsDMARDs should be screened for infections including active and latent tuberculosis, Hepatitis B (with HepBs antigen, HepBs antibody and HepB core antibody), Hepatitis C and HIV (in high-risk population) before initiating targeted therapy. Patients with active or latent infections should receive adequate therapy for these infections. Serum immunoglobulins are also checked prior to rituximab therapy because it further increases the risk of infections in patients with hypogammaglobulinemia. Blood pressure should be checked prior to starting leflunomide and if it is > 140/90 mmHg on two consecutive readings 2 weeks apart, hypertension should be treated prior to commencing RA therapy.

12. How should patients on DMARDs be monitored?

Monitoring of patients include assessing disease activity, observing for side effects of therapy and complications of the disease. Disease activity should ideally be assessed using validated tools such as DAS-28 and documented at each review. As a general principle, monitoring should be more frequent when treatment is first started or when the dose is increased. Once the patient is stable on a particular dose for a period of time, monitoring frequency can be reduced. If a

patient is on combination therapy, more frequent monitoring is needed and must be guided by clinical judgement. Elucidating common and serious side effects and monitoring of patients on different DMARDs used in the treatment of RA are beyond the scope of this article, and Sri Lanka does not have any institution or national level guidelines on it yet. However, these details can be easily found in any accepted formulary or in the product literature.

13. Can DMARDs be tapered or discontinued?

Studies have demonstrated that there is a moderate-to-high risk of a disease flare with withdrawal of DMARDs and there is potential for irreversible long-term damage even with grumbling untreated disease. Therefore, continuation of all DMARDs at their stable dose is preferred over a dose reduction. If a patient is persistently on target for a period of time, the dose may be reduced based on patient and physician preferences and expectations, bearing in mind the risks involved. Although there is no established optimal time at target prior to tapering, most consider a minimum of 6 months to be a reasonable duration of time.

The choice of DMARD for gradual discontinuation in patients who are on combination therapy is also preference sensitive and it is often based on cost and tolerability. In general, gradual discontinuation of SSZ over discontinuation HCQ or MTX is preferred in those on triple therapy due concerns of long-term tolerability of SSZ. For patients on a bDMARD or tsDMARD in combination with MTX or another csDMARD, some prefer to taper (either to reduce the dose or increase the dosing interval) of bDMARD or tsDMARD considering the cost and safety profiles, while others prefer gradual discontinuation of the csDMARD. Nevertheless, maintaining a therapeutic dose of at least one DMARD is preferred over gradual discontinuation of all DMARDs.

14. What is the place of NSAIDs in the management of RA now?

The use of NSAIDs is ubiquitous in rheumatology because of their analgesic and anti-inflammatory actions. However, in current practice NSAIDs are primarily limited to symptomatic relief of pain in RA. NSAIDs are particularly useful if the pain is due to a cause other than active synovitis such as concomitant osteoarthritis or soft tissue problems. Although NSAIDs may be effective against minor inflammation, a short course of steroids or IM steroid injections may work better for patients with a RA flare while DMARDs are being adjusted. Nevertheless, long term use of NSAIDs is best avoided and one must be mindful of drug interactions when prescribing for patients with RA because they are likely to be on multiple medications.

15. What DMARDs can be used to treat RA in pregnant or breast-feeding women?

RA disease activity improves substantially during pregnancy in many women. Conversely, some develop flares and have persistently active disease throughout their pregnancy. Therefore, all women with preexisting RA who are planning to become pregnant should receive pre-conception counselling. All pregnancy-incompatible drugs should be avoided in them. In women who are already on DMARDs planning pregnancy, DMARDs that are contra-indicated during pregnancy should be switched to a pregnancy-compatible alternative in advance to ensure maintenance of good disease control on the new medication.

HCQ and SSZ are compatible with both pregnancy and lactation. Other DMARDs which can be used during pregnancy and breastfeeding although not routine used for the treatment of RA include azathioprine, ciclosporin, and tacrolimus. MTX and LEF are contra-indicated during pregnancy and lactation. If a woman on MTX is planning pregnancy, it should be stopped 3 months in

advance of planned conception. This duration has been reduced to 1 month in a recent British Society of Rheumatology guideline, because of emerging evidence from registries and cohort studies that suggests inadvertent MTX exposure in the first trimester may not significantly increase the risk of congenital malformations, fetal death or neonatal complications (10). Women on LEF should stop that drug and undergo cholestyramine washout until plasma levels are undetectable prior to conception.

With regard to biologics, TNF inhibitors are generally acceptable during pregnancy and lactation. Due to limited evidence, it is recommended that rituximab, IL-6 inhibitors and abatacept be stopped at conception although these have not been shown to be teratogenic. They are considered compatible with breast milk exposure based on limited evidence available. JAK inhibitors should be stopped at least 2 weeks prior to conception and should be avoided during lactation.

Summary

- RA is clinical diagnosis based on clinical features, serological markers, and radiological features. Joint ultrasound and MRI are useful to detect early changes.
- DMARDs should be started as soon as a diagnosis of RA is made.
- The aim is to achieve remission or low disease activity in every patient and therapy should be adjusted if there is no improvement by 3 months or patient is not at target by 6 months of starting treatment.
- MTX is the drug of first choice in treatment naïve patients with moderate-to-high disease activity unless contra-indicated.
- If MTX is contra-indicated or not tolerated LEF or SSZ is preferred over other csDMARDs as an initial treatment strategy.
- HCQ can be used in the treatment naïve patients with low disease activity.
- Short courses of glucocorticoid in the lowest effective dose can be used as bridging therapy until the DMARDs take effect.
- Addition of a bDMARD or a tsDMARD is recommended for patients taking maximally tolerated doses of MTX who are not at target. Dual or triple combination therapy of csDMARDs is also an acceptable option particularly if there are no poor prognostic factors.
- Switching to a bDMARD or tsDMARD of a different class is recommended for patients taking a bDMARD or tsDMARD who are not at target.
- Pre-treatment evaluation includes screening for latent or active infections particularly in those who are to be started on bDMARDs or tsDMARDs.
- Patients should be monitored periodically to assess disease activity and side effects of therapy.
- Maintaining a therapeutic dose of at least one DMARD is preferred over gradual discontinuation of all DMARDs even in patients with persistent sustained remission.
- DMARDs should be switched to those compatible with pregnancy in advance in women planning pregnancy. MTX and LEF are contra-indicated during pregnancy and lactation. HCQ, SSZ and azathioprine are compatible with pregnancy and lactation. TNF inhibitors are also acceptable in pregnancy and lactation.

References

1. Taylor PC. Update on the diagnosis and management of early rheumatoid arthritis. Clin Med (Lond). 2020;20(6):561-4.

2. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-81.

3. Di Matteo A, Mankia K, Azukizawa M, Wakefield RJ. The Role of Musculoskeletal Ultrasound in the Rheumatoid Arthritis Continuum. Curr Rheumatol Rep. 2020;22(8):41.

4. van Nies JA, Tsonaka R, Gaujoux-Viala C, Fautrel B, van der Helm-van Mil AH. Evaluating relationships between symptom duration and persistence of rheumatoid arthritis: does a window of opportunity exist? Results on the Leiden early arthritis clinic and ESPOIR cohorts. Ann Rheum Dis. 2015;74(5):806-12.

5. Smolen JS, Landewe RBM, Bergstra SA, Kerschbaumer A, Sepriano A, Aletaha D, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023;82(1):3-18.

6. Fraenkel L, Bathon JM, England BR, St Clair EW, Arayssi T, Carandang K, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2021;73(7):924-39.

7. Ranganathan P, Eisen S, Yokoyama WM, McLeod HL. Will pharmacogenetics allow better prediction of methotrexate toxicity and efficacy in patients with rheumatoid arthritis? Ann Rheum Dis. 2003;62(1):4-9.

8. Faarvang KL, Egsmose C, Kryger P, Podenphant J, Ingeman-Nielsen M, Hansen TM. Hydroxychloroquine and sulphasalazine alone and in combination in rheumatoid arthritis: a randomised double blind trial. Ann Rheum Dis. 1993;52(10):711-5.

9. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med. 1995;333(3):142-6.

10. Russell MD, Dey M, Flint J, Davie P, Allen A, Crossley A, et al. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford). 2023;62(4):e48-e88.

Dr. Chiranthi Liyanage
MBBS, MD, MRCP (UK), MRCP (UK) (Rheumatology), PgCertMedEd
Specialist in Rheumatology and Rehabilitation, Senior Lecturer, Department of Pharmacology, Faculty of Medicine, University of Colombo.

Self-Assessment Questions

1. A 31-year-old female with rheumatoid arthritis presents with a severe disease flare 2 months post-partum. She is currently on sulfasalazine 1g three times a day and hydroxychloroquine 200 mg daily. What is the most appropriate immediate next step in her management?

A. Add methotrexate 15 mg weekly
B. Add naproxen 250 mg twice a day
C. Increase hydroxychloroquine dose to 200 mg twice a day
D. Start adalimumab 40 mg fortnightly
E. Start prednisolone 10 mg daily

2. A patient on methotrexate 20 mg weekly for seropositive rheumatoid arthritis is started on trimethoprim-sulfamethoxazole for prophylaxis of recurrent cystitis. I week later, she presents with fever with chills and rigors, and she is found to have a neutrophil count of neutrophil count of 1200/microL. What is the most likely mechanism responsible for her current presentation?

A. A type B adverse drug reaction to trimethoprim-sulfamethoxazole
B. Autoantibodies neutralizing granulocyte colony-stimulating factor
C. Autoimmune destruction in the peripheral circulation
D. Pharmacodynamic synergism with trimethoprim-sulfamethoxazole
E. Sequestration in the spleen

3. A patient with rheumatoid arthritis who sulfasalazine 1g twice daily and methotrexate 10 mg weekly is awaiting the 4th booster dose of the COVID vaccine. What advice should be given to her regarding her medicines when getting the COVID booster?

A. Continue both methotrexate and sulfasalazine
B. Defer the COVID booster till the patient is off DMARDs for 1 year
C. Stop all DMARDs 2weeks prior to receiving the vaccine
D. Stop methotrexate and continue sulfasalazine 2 weeks prior to vaccination
E. Stop sulfasalazine and continue methotrexate 2 weeks prior to vaccination

Self-Assessment Questions - Answers

1. E

Methotrexate is contraindicated during lactation. Hydroxychloroquine has only a weak effect on rheumatoid arthritis, thus increasing the dose is unlikely to be beneficial. Furthermore, the clinical effect of both methotrexate and hydroxychloroquine will not show any beneficial clinical effect for a few weeks. Naproxen might not result adequate pain relief as the patient is having a severe flare and it will not have any effect on disease progression. Starting a TNF inhibitor is reasonable the next step in management of this patient. However, this might not be possible immediately because the patient will have to undergo relevant pre-treatment screening (Hepatitis B, C, HIV, latent TB etc.) prior to commencement of a TNF inhibitor. Therefore, the most appropriate next immediate step would be a add a steroid till the pre-treatment workup is complete.

2. D

Whilst all mechanisms could cause a neutropenia in a patient with seropositive rheumatoid arthritis, the most likely cause in this case is trimethoprim-sulfamethoxazole increasing the toxicity of methotrexate through pharmacodynamic synergism as both drugs inhibit the dihydrofolate reductase enzyme and thereby inhibit purine synthesis and cell proliferation.

3. A

All current COVID-19 vaccines are non-live vaccines and these can be administered to patients on DMARDs and glucocorticoids. However, the immunological response may not be as robust as expected due to the immunosuppressive effect of these medicines. However, sulfasalazine is less immunosuppressive compared to other DMARDs and the methotrexate in doses over 0.4mg/kg/week is considered immunosuppressive whilst doses less than this produces only low-grade immunosuppression. Therefore, both methotrexate and sulfasalazine can be continued in this patient.

Erectile dysfunction: causes, assessment and management options

Summary

Erectile dysfunction is one of the most common male sexual dysfunctions. The diagnosis can usually be made by a detailed history and examination. Men with erectile dysfunction benefit from multimodal management strategies. These include lifestyle modification, medical treatment and psychosexual counselling and therapy. An oral phosphodiesterase-5 inhibitor is often prescribed for erectile dysfunction. Providing simple and clear instructions is critical to realise the full benefits of these drugs. Those with severe vascular disease or a history of pelvic surgery may not respond to phosphodiesterase-5 inhibitors. Anxiety or unrealistic expectations can also result in a poor response.

Keywords : erectile dysfunction, impotence, phosphodiesterase-5 inhibitors

(Aust Prescr 2022;45:159–61)

Introduction

Erectile dysfunction is a prevalent sexual dysfunction in men.[1] Male sexual dysfunction can occur at any age, but erectile dysfunction and diminished libido increase with age. There may be underlying causes.

Multimodal management is needed, but when drugs are indicated, oral phosphodiesterase-5 inhibitors or self-injectables such as alprostadil are options for erectile dysfunction.

It is important to initially discuss treatment objectives and outcomes, and set realistic expectations to avoid dissatisfaction. While there is information available about drugs to use in erectile dysfunction, the information is rarely accompanied with specific advice for the patient on timing and other details about how to use the drugs.

Erectile dysfunction

Men with erectile dysfunction are unable to achieve an erection firm enough for sexual intercourse.

Causes

There are many causes and risk factors for erectile dysfunction (Box 1).[2] These were traditionally classified as organic, psychogenic or mixed. However, with advancements in the fields of psychological science and sexual medicine, the current view is that the aetiological factors are multimodal[3] – biological, psychological, sociocultural, relational and sexual.

Assessment

Men presenting with erectile dysfunction are initiallyassessed with a comprehensive history (Box 1). This helps the clinician to understand and differentiate the causes as predisposing (why this person?), precipitating (why now?) and perpetuating (what is keeping the problem?) factors. The history includes lifestyle (quality and quantity of sleep, snoring and sleep apnoea, weight, exercise, alcohol, smoking history), general health (physical and mental, medicines) and a relationship and psychosexual history.[4,5] Box 2 shows some key questions to ask. Eliciting details about the quality of morning erections and erectile capacity during other sexual activities (e.g. masturbation) are critical to understand the underlying aetiology.[4] The history of past and current treatment for erectile dysfunction, and the response achieved, helps in tailoring further management.

A distinction must be made whether the man has erectile dysfunction or premature ejaculation because some men are not good at describing their problem. The man with premature ejaculation may say he has erectile dysfunction because he loses his erection early after ejaculation. Conversely, the man with erectile dysfunction may complain of premature ejaculation as he rushes to ejaculate quickly before he loses his erection. Erectile dysfunction and premature ejaculation are often confused but can occur together.

The history should include a review of medicines (as listed in Box 1). This could provide valuable insight about the sexual adverse effects of certain drugs and, more importantly, a timeline between starting a specific drug and the onset of erectile complaints.

The physical examination should include, at a minimum, general parameters (weight, waist circumference, body mass index and blood pressure) and the genitals. If investigations are indicated, the minimum is serum lipids, fasting glucose or ideally glycated haemoglobin.[4,5] Should hypogonadism be suspected, measure serum testosterone on a blood sample taken before 11 am.[4]

A validated questionnaire, for example the International Index of Sexual Function (IIEF-5),[6] can be an adjunct to history and examination. However, such questionnaires should not be used alone for diagnosing erectile dysfunction.[5]

Box 1 ***Risk factors for erectile dysfunction***

- Advanced age
- Atherosclerosis-related risk factors (e.g. cardiovascular disease, cigarette smoking, hypertension, dyslipidaemia, diabetes mellitus)
- Pelvic surgery (e.g. radical prostatectomy), radiation, trauma
- Endocrinological conditions (e.g. hypogonadism, hyperprolactinaemia, thyroid disorder)
- Obesity and metabolic syndrome
- Substance abuse – alcohol, illicit drugs (e.g. cannabis, barbiturates, cocaine, heroin, methamphetamine)
- Psychological (partner-related, stress, guilt, situational anxiety, self-image problems, low self-esteem, history of sexual abuse, highly restricted sexual upbringing, generalised anxiety disorder, depression, psychosis)
- Erectile dysfunction associated with other sexual dysfunction(s) (e.g. premature ejaculation, sexual aversion disorder, anorgasmia)
- Medicines:
  - antihypertensives (e.g. diuretics, alpha and beta blockers)
  - psychotropics (e.g. selective serotonin reuptake inhibitor and other antidepressants, antipsychotics, anxiolytics)
  - anticonvulsants, anti-Parkinson's drugs
  - hormone-affecting drugs – antiandrogens, corticosteroids, chronic opioid use
- Neurological conditions (Alzheimer's disease, multiple sclerosis, Parkinson's disease, stroke), spinal cord and peripheral nerve disorders (diabetic neuropathy)
- Penile abnormalities (e.g. Peyronie's disease, venous leak)

Box 2 ***Key questions in the assessment of erectile dysfunction***

- Is the problem intermittent, global or situational?
- Is the problem recent or long term?
- Is there an unusual curvature of the erection or an episode of sexual trauma to the erect penis?
- Has the patient ever suffered from mental health problems?

Management options

The initial treatment of erectile dysfunction addresses lifestyle changes and psychological or relationship problems. Sex therapy is indicated particularly when there is a significant psychological contribution to erectile dysfunction and when there is no response to medical management.7 Ideally, sex therapists should be healthcare professionals with specific qualifications in the field of human sexuality along with skills in counselling and psychosexual therapy. General practitioners, psychologists and sexual health physicians can offer certain aspects of sex therapy, whereas a well-qualified and trained sex therapist can offer comprehensive psychosexual education, counselling and therapy.

Phosphodiesterase-5 inhibitors

The first step of drug treatment is an oral phosphodiesterase-5 inhibitor:
- sildenafil 25, 50 and 100 mg
- vardenafil 5 and 20 mg
- avanafil 50, 100 and 200 mg
- tadalafil 5, 10 and 20 mg.

Phosphodiesterase-5 inhibitors work best if taken 1–2 hours before sexual intercourse. Tadalafil has a two-hour lead-in time, when taken as required, so is often used as a daily low-dose (5 mg) treatment. Daily dosing may also benefit men with erectile dysfunction who have benign prostatic hyperplasia as it can improve lower urinary tract symptoms.
Large meals and alcohol should be avoided before a dose, but when phosphodiesterase-5 inhibitors are taken daily, food and alcohol have less impact on the response. It is critical to educate patients that phosphodiesterase-5 inhibitors do not create sexual stimuli. They only help with getting and maintaining an erection when there is adequate external sexual stimulation.
Depending on the severity of erectile dysfunction, the clinician decides on the appropriate starting dose. Importantly, patients should be made aware that they need to take the drug as prescribed and, on five to six occasions, to assess the treatment effect. Failure to provide this information could lead to a suboptimal or no response, which in turn could lead to an inappropriate use of higher doses or the addition of other treatment options. The response to phosphodiesterase-5 inhibitors can be affected by anxiety, alcohol, excessive expectations of how these drugs should work, and not waiting long enough for them to work. The American Urological Association Guideline states that sildenafil, tadalafil, vardenafil and avanafil have similar efficacy in men with erectile dysfunction and that dose-response effects across phosphodiesterase-5 inhibitors are small and nonlinear.8 While there is no firm evidence that switching from one phosphodiesterase-5 inhibitor to another will have a beneficial effect, it is worth a clinical attempt provided the expectations are discussed with the patient.The classic adverse effects of phosphodiesterase-5 inhibitors are flushed face, headaches, blocked nose, altered colour vision (mainly with sildenafil) and gastric reflux. Most of these adverse effects have a dose-response pattern. The average rates are similar across the phosphodiesterase-5 inhibitors except for dyspepsia (lowest rates reported with avanafil), flushing (lowest rates reported with tadalafil), and myalgia (lowest rates reported with vardenafil and avanafil).8 Tadalafil is associated with low back and leg pain which often go away when the drug is stopped.Phosphodiesterase-5 inhibitors should not

be prescribed if the patient is taking nitrates or uses 'recreational' amyl nitrite. There is a risk of a precipitous blood pressure drop.

Injectable drugs

Penile injections tend to be used when oral phosphodiesterase-5 inhibitors are not effective. The drugs used for intracavernosal penile injection are vasoactive. They include alprostadil, which may be combined with papaverine and phentolamine. Penile injections work rapidly so sexual activity may begin within 10–15 minutes of injecting.Care must be taken to use the lowest effective dose to avoid priapism which can be a medical emergency. The patient may also experience delayed post-injection pain. Patient education (by means of explaining or referring to product information, or video demonstrations) is very important. The drug needs to be injected into the shaft at 10 o'clock or 2 o'clock positions, altered between different attempts, avoiding obvious veins and fibrosis. Devices High rates of patient satisfaction have been reported for vacuum erection devices. They can be an effective and low-cost treatment option for any men with erectile dysfunction but more so for those with diabetes, spinal cord injury or after prostatectomy.8Older men may tend to use vacuum mechanical devices as they are drug free. However, vacuum erection devices can be cumbersome and require some training in correct use. Shockwave therapy applies acoustic shock waves to the penis. This aims to improve vascularisation. Shockwave therapy appears to work best for the older patient with vasculogenic erectile dysfunction, but lacks robust evidence of efficacy.9 A penile implant is a restorative treatment option. It is a very effective treatment no matter the aetiology
or severity of the erectile dysfunction and even if all other treatments have failed or are not suitable. However, it is irreversible.

Evaluation of treatment outcomes

Evaluating treatment outcomes for erectile dysfunction depends on the management goals that were established before treatment. Erectile capacity across different sexual activities (intercourse, masturbation), quality of morning erections, reduction in distress and overall sexual satisfaction are some of the measures used to assess progress.

Conclusion

Erectile dysfunction is a common male sexual dysfunction. It requires a comprehensive clinical assessment and multimodal management. This may involve GPs, specialists and allied health professionals trained in the field of sexology

References

1. Hatzimouratidis K, Amar E, Eardley I, Giuliano F, Hatzichristou D, Montorsi F, et al.; European Association of Urology. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. Eur Urol 2010;57:804-14. https://doi.org/10.1016/j.eururo.2010.02.020

2. Shoshany O, Katz DJ, Love C. Much more than prescribing a pill - assessment and treatment of erectile dysfunction by the general practitioner. Aust Fam Physician 2017;46:634-9.

3. Hatzichristou D, Kirana PS, Banner L, Althof SE, Lonnee-Hoffmann RA, Dennerstein L, et al. Diagnosing sexual dysfunction in men and women: sexual history taking and the role of symptom scales and questionnaires. J Sex Med 2016;13:1166-82. https://doi.org/10.1016/j jsxm.2016.05.017

4. Wylie KR, editor. ABC of sexual health. 3rd ed. Hoboken (NJ): Wiley; 2015.

5. Rew KT, Heidelbaugh JJ. Erectile dysfunction. Am Fam Physician 2016;94:820-7.

6. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Peña BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 1999;11:319-26. https://doi.org/10.1038/sj.ijir.3900472

7. Ramanathan V, Redelman M. Sexual dysfunctions and sex therapy: the role of a general practitioner. Aust J Gen Pract 2020;49:412-5. https://doi.org/10.31128/AJGP-02-20-5230

8. Burnett AL, Nehra A, Breau RH, Culkin DJ, Faraday MM, Hakim LS, et al. Erectile dysfunction: AUA guideline. J Urol 2018;200:633-41. https:// doi.org/10.1016/j.juro.2018.05.004

9. Gruenwald I, Appel B, Kitrey ND, Vardi Y. Shockwave treatment of erectile dysfunction. Ther Adv Urol 2013;5:95-9. https://doi. org/10.1177/1756287212470696

Michael Lowy
Sexual health physician, Double Bay, Sydney

Vijayasarathi Ramanathan
Lecturer in Sexual Health, University of Sydney

Reproduced with permission from Aust Prescr (Aust Prescr 2022;45:159–61)

ISSN 1391-0736

COLOMBO
UNIVERSITY PRESS