

Rheumatoid Arthritis Refractory to DMARDs: A Case Study

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Case Report

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Abstract

In past few years there has been an enthusiastic progress in the field of rheumatoid arthritis pharmacotherapy but the presence of prognostic factors associated with unfavorable outcomes and the inappropriate and/or delayed initiation of DMARDs may diminish the likelihood of achieving remission and/or increase the probability of refractoriness to treatment.

Keywords: Rheumatoid arthritis; Unfavorable outcomes; Refractory patients; DMARDs; Biologics

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease whose main characteristic is persistent joint inflammation that results in joint damage and loss of function. It is an inflammation of synovial tissue with symmetric involvement of peripheral joints, hand, feet, and wrists being most commonly affected. RA can also affect non-articular muscular structures such as tendons, ligaments, and fascia [1].

Approximately 1% of the population worldwide is affected by RA, with females being two to three times more commonly affected. The prevalence of RA increases with age in both sexes; nearly 5% of women and 3% of men over the age of 65 years are affected by the disease [2]. The prevalence of RA varies widely from population to population, with the lowest rates in Asian countries and higher rates among certain Native American populations and this proves that there is some genetic component underlying susceptibility to RA [3]. The incidence of RA increases with increasing age in most

populations until about the eighth decade of life, when it declines [4]. The peak age of incidence is about 30-50 years in women and slightly older in men [1].

RA also affects young children and its classification and treatment differs slightly from adults. The cause of RA remains unclear with the hormonal, genetic environmental and lifestyle factors playing key roles. Genetic factors contribute 53-65 % of the risk of development of this disease and the HLA-DR4 allele is associated with both the development and severity of RA. Cigarette smoking is a strong risk factor for developing RA. It affects not only the joints but a wide range of extra-articular organs. Although RA is more common in females, extra-articular manifestations of the disease are more common in males. The extra-articular manifestations of RA can occur at any age after onset. It is characterized by destructive polyarthritis and extra-articular organ involvement, including the skin, eye, heart, lungs, kidneys, nervous and gastrointestinal systems. The frequency of extra-articular manifestations in RA differs from one country to another. Extra-articular organ involvement in

RA is more frequently seen in patients with severe, active disease and is associated with increased mortality [1].

Pharmacological treatment includes NSAIDs [Non-selective (aceclofenac, acemetacin, diclofenac, ibuprofen, naproxen, piroxicam, tiaprofenicacid) COX-2 inhibitors (celecoxib, etoricoxib)], Glucocorticoids [prednisolone, methylprednisolone, triamcinolone (used as bridging therapy as DMARDs take several months to take effect)] DMARDs [auranofin, azathioprine, ciclosporin, HCQ, leflunomide, MTX, sodium aurothiomalate, sulphasalazine] and Biologics [adalimumab, cetrolizumabpegol, entercept, anakinra, rituximab]. Non-pharmacological treatment is of great importance in RA patients as it is a chronic condition requiring continuous care and life style modifications including physiotherapy, occupational therapy, psychological support & employment counseling [1].

Refractory disease is defined as the failure to attain a predefined target, which is accepted to be remission or, at least, a low disease activity state of the disease. Despite of the enthusiastic progresses in the field of RA pharmacotherapy, few patients are still reaching sustained remission. Refractoriness can be mitigated by tight monitoring and early use of both synthetic and

biologic DMARDs aiming remission at each individual patient [5].

Case Presentation

A 46 years old married woman who was a known patient of RA for 10 years and diabetes type 2 for 3 years was admitted to the department of rheumatology in a public hospital. She was a housewife, mother of 3 children and belonged to Sargodha. She has BMI of 27.34 kg/. She was on regular medication but her symptoms have been worsening for the past 6 months and experienced early morning sickness that lasts for more than 1 hour. Her presenting complaint was severe pain, inflammation and stiffness in multiple joints of hands, shoulders, back, knees, wrists & ankles. She also complained about on and off fever, difficulty in walking and burning micturition. She has no history of photosensitivity, rash, oral ulcer, SOB or blur vision.

Investigations

BP 130/80, Pulse 100/min, Temp 99°F, R.R 20/min BP. Musculoskeletal: ROM normal but restricted due to pain. No scar mark. No lesions.

Tests	Normal Ranges	Units	Values
Rheumatoid factor	< 14	IU/ml	21
Anti-ds DNA (anti-double stranded DNA)	< 20	IU/ml	30
ESR (wintergreen method)	0-20	mm/1 st hour	115
Anti-CCP Antibody(anti-cyclic citrullinated peptide)	< 20	U/ml	91
Hb (hemoglobin)	11.1-14.5	g/dl	8.9
CRP (C-reactive protein)	0-3	mg/dl	6
Fasting plasma glucose test	< 100	mg/dl	200

Past Medication History

Methotrexate 20mg/week,
Salazodine EC 3g/day,
Hydroxychloroquine 500mg/day
Oral hypoglycemic agents.

Assessment

- Patient never had complete resolution of symptoms
- RA e⁻ Flare
- Range of movement restricted
- Disease Refractory to DMARDs
- Anaemia
- Uncontrolled DM-2
- Burning micturition (probable cause; UTI)

Treatment

Treatment Plan for Uncontrolled DM-2

Send HBA1C
Tab. Minidiab 5mg PO×OD
BSL×TDS×ISS

Treatment Plan For Rheumatoid Arthritis

Start inj. Solumedrol 500 mg in 100 ml NS over 4 hours
Inj. Doplet – 3 200000 IU PO×STAT
Tab. Osnate – D PO×OD 6am
Tab. Nuberol PO×BD 6am & 6pm
Tab. Annuva 50 mg PO×BD 6am & 6pm
Inj. Risek 40 mg IV×OD 10am
Tab. Terlax 2 mg 1 ½ OD×HS 10pm
Tab. Multiplex – M PO×OD(in evening) 6pm
Cap. Sangobian PO×OD 6am

Outcome & Follow-up

- Follow up with therapy.
- Symptom relief including pain control.
- Slowing or prevention of joint damage.
- Preserving and improving functional ability.
- Achieving and maintaining disease remission.
- Blood sugar level control as the patient is also diabetic.
- Restoring blood hemoglobin level to normal.
- Relief from burning micturition.
- Routine monitoring of blood tests, urine tests, blood pressure, blood sugar level and weight checks.
- Consultation with rheumatologist every 3 months. Counsel the patient to stick to the drug regimen and to show good compliance.
- Routinely monitoring of complete blood count, blood pressure, creatinine clearance, liver function tests, urinalysis, weight check and blood sugar levels.
- Annual review with optometrist.
- Physiotherapy sessions to enhance joint flexibility and muscle strength [6].
- Avoid contact with people who have infections that may spread to others (such as chickenpox, measles, flu). Consult your rheumatologist if exposed [7].
- Do not have immunizations, vaccinations or skin tests without the consent of your rheumatologist [8].

Discussion

Suggest rheumatologist to add biologicsto therapy as disease is refractory to DMARDs. The patient complained of burning micturition which is due to UTI either because of RA or most possibly due to DM as sugar in the urine makes for a fertile breeding ground for bacteria [9]. So, suggest the physician to prescribe a suitable antibiotic like Ceftriaxone. Using Solumedrol (methylprednisolone) and diclofenac sodium together may increase the risk of side effects in the gastrointestinal tract such as inflammation, bleeding, ulceration and rarely perforation so take diclofenac sodium with food to lessen the risk and never skip omeprazole. Also suggest the physician to alter the timings to ensure gap of 2 hours between Solumedrol and diclofenac sodium.

Avoid consuming grapefruit juice while on Solumedrol as it may increase the blood levels of methylprednisolone. Solumedrol interferes with blood glucose control and reduce the effectiveness of glipizide and Regular Insulin. So blood glucose levels need to be monitored closely. Although the patient's BSL is being monitored regularly but the patient will be going to need adjustment of anti-diabetic medications even after stopping Solumedrol. Diclofenac sodium can increase the effects of glipizide and cause hypoglycemia so very close monitoring is advised.

The sedative effect of tizanidine may be potentiated by concomitant use of orphenadrine citrate & paracetamol. The maximum number of medicines in the non-narcotic analgesics category to be taken concurrently is usually two. The list included four medicines belonging to this category: diclofenac sodium, orphenadrine citrate & Paracetamol), tizanidine. The recommended maximum number of medicines in the muscle relaxantscategory to be concurrently taken is usually one. This list includes two belonging to this category: Orphenadrine citrate & Paracetamol and Tizanidine. However, the benefits of taking this combination of medicines outweigh any risks associated with therapeutic duplication.

Recommendations

- o NICE and rheumatology organizations in the UK and Europe recommend that people with rheumatoid arthritis should first be treated with conventional DMARDs, one of which is usually methotrexate, and that the dose should be carefully adjusted to achieve as much improvement as possible as quickly as possible. If this is not successful after six months, and you have high disease activity you may be eligible for a first-line biologic drug (this includes all of the anti-TNF drugs and tocilizumab) on the NHS [10].
- o Anti-TNF therapy is also associated with an increased risk of shingles, and may increase the risk of some unusual infections, in particular tuberculosis (TB), salmonella and listeria. Because we know this, we can take steps to minimize those risks. For example, the patient must be screened for TB before startingtreatment, and advised to avoid possible sources of salmonella and listeria such as undercooked meats and eggs or unpasteurized foods [10].
- o An appropriate choice of treatment among anti-TNF for this patient is a higher dose infliximab (10 mg/kg) in combination with methotrexate appeared to be more effective than the standard 3 mg/kg dose, particularly for the patients with a severe disease activity. The benefits of this high-dose treatment appeared to become evident over time, and those patients who received higher doses of infliximab did not experience a higher incidence of severe adverse events. The addition of oral low-dose steroids significantly enhanced infliximab efficacy and is more beneficial in this case [11].

Conclusion

Refractory disease in patients with acute flare needs to be controlled by using DMARDs combined with Biologics in order to attain sustained remission in susceptible

patients. Early and optimized use of DMARDs and Biologics, close monitoring of symptoms, adherence to therapy, routine monitoring of hepatic and renal function, regular exercise and timely consultation with rheumatologist ultimately leads to reduced probability of refractoriness to treatment.

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