<table>
<thead>
<tr>
<th>Section 16: Rheumatology and CTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>206. Refractory Rheumatoid Arthritis</td>
</tr>
<tr>
<td>Rohini Handa</td>
</tr>
<tr>
<td>207. Difficulties in Rheumatoid Arthritis</td>
</tr>
<tr>
<td>Rajan Kumar</td>
</tr>
<tr>
<td>208. Monoarthritis—A Clinical Dilemma to Internists</td>
</tr>
<tr>
<td>Arup Kumar Kundu, Abhishek Kundu</td>
</tr>
<tr>
<td>209. Oral Targeted Treatments in RA—Update 2021</td>
</tr>
<tr>
<td>Ramakrishna Rao Uppuluri, Sripurna Deepti Challa</td>
</tr>
<tr>
<td>210. Biosimilars: Bane or Boon for India</td>
</tr>
<tr>
<td>Durga Prasanna Misra, Pallavi Patro, Vikas Agarwal</td>
</tr>
<tr>
<td>211. An Approach to Vasculitis</td>
</tr>
<tr>
<td>Packiamary Jerome</td>
</tr>
<tr>
<td>212. How to Manage DMARDs Failure in RA?</td>
</tr>
<tr>
<td>N Subramanian</td>
</tr>
<tr>
<td>213. IgG4-related Disease</td>
</tr>
<tr>
<td>Harpreet Singh, Somdatta Giri, Anju Arya</td>
</tr>
</tbody>
</table>
Abstract
A sizeable number of patients with rheumatoid arthritis (RA) are unable to attain low disease activity or remission despite treatment. These difficult to treat (D2T) patients are labeled as refractory RA. The troika of D2T RA, as outlined by the European League against Rheumatism, comprises of treatment failure history, presence of active/symptomatic disease, and clinical perception. The approach to refractory RA is evolving.

Introduction
Rheumatoid arthritis (RA) is the commonest inflammatory polyarthritis seen in clinical practice. Current management paradigms use a "treat to target" stratagem to achieve tight disease control. The conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) led by methotrexate form the initial treatment. A better understanding of the disease, pathobiology has led to the development of several targeted treatments, which are broadly divided into two categories: biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs). Despite tremendous advances in disease assessment, and an ever-expanding treatment armamentarium, a significant proportion of patients are unable to achieve optimal disease control. This group of "refractory" patients poses a challenge to the immunologists from a mechanistic angle, to rheumatologists from the perspective of disease definition, and to all clinicians from a treatment viewpoint. This chapter outlines the approach to refractory RA from a clinical standpoint.

Definition of Refractory RA
The definition of refractory RA is imprecise as different authors, in absence of a consensus, have defined it differently. The analogy that I often use is "pyrexia or fever of unknown origin" (PUO/FUO) that was initially defined as a condition in which the core body temperature is >38.3°C for a period of three weeks or more, with no diagnosis reached after 1 week of "inpatient investigation." The quantum and extent of investigations were not spelt out. Also, modern day health care has moved away from hospitalization for investigations. The revised definition of PUO—"persistent fever that remains undiagnosed despite 1 week of hospital evaluation or three outpatient visits" also suffers from lack of specificity. Much in the same way, the definition of refractory RA continues to elude consensus.

Simply put, refractory RA is disease that continues to be active despite adequate treatment for sufficient time. The lack of uniformity stems from the fact that refractory RA has three dimensions: disease activity, adequacy of treatment, and time. The concept of disease activity is a quantitative target with reasonably well defined variables. Validated indices like simplified disease activity index (SDAI) and clinical disease activity index (CDAI) are available and widely used in rheumatology clinics. Their use is overtaking the use of DAS 28 (disease activity score 28). A detailed exposition of various disease activity measures is beyond the scope of this chapter. Briefly, SDAI
is simple numerical summation of swollen joint count (SJC)-28 joints, tender joint count (TJC)-28 joints, CRP in mg/dL (range 0.1–10), patient’s global disease activity on a 10-cm visual analogue scale (VAS) and physician’s global assessment on a 10-cm VAS. The CDAI excludes CRP. DAS 28 requires four simple inputs: 28 TJC, 28 SJC, ESR, and general health (GH) assessment by the patient on a VAS from 0 to 100. The formula used is: DAS 28 = 0.56√TJC + 0.28√SJC + 0.7 ln ESR + 0.014 GH. Online calculators and apps are available for calculation. The cut offs are mentioned in Table 1. The goal of treatment is remission (Table 2), failing which low disease activity (LDA) is an acceptable alternative.

The second operational component—time taken to achieve LDA/remission—has undergone a sea change. Older publications talk about early disease as a disease duration of 2 years. Current recommendations like European League against Rheumatism (EULAR) and American College of Rheumatology talk about early RA as a disease duration less than 6 months. They also emphasize that clinicians should aim for clinical remission (ACR-EULAR criteria) or at least low disease activity within 6 months (of which about 80% improvement of disease activity should be within 3 months of starting treatment). It is recommended that if there is no improvement by at most 3 months after the start of treatment, or the target has not been reached by 6 months, therapy should be adjusted.

It is the third component of the definition—adequate treatment—that is a matter of debate. Recent clinical trials define refractory RA as “moderately to severely active RA (≥6 tender joints of 68 joints examined, ≥6 swollen joints of 66 joints examined, and a serum CRP level ≥3 mg per liter) and patients must have previously received one or more TNF inhibitors and discontinued treatment because of an insufficient response after 3 months or more or because of unacceptable side effects.” Other authors define refractory RA as patients who have experienced three treatment courses (with at least one biological) over a minimum of 18 months since diagnosis without reaching the treatment goal of low disease activity or remission.

To make matters complex, some authors have proposed that non-responders be classified into “primary” and “secondary” non-responders. The latter, after the initial response to the drug, stop responding after a variable period of time. In some of these, anti-drug antibodies (ADA) to the biologics may be responsible for the secondary non-response. This has been termed “pharmacokinetic refractoriness” to differentiate it from intrinsic refractoriness in the primary non-responders.
It is to be noted that not all secondary non-response are due to ADA. Also, ADA are seen with biologics, which are foreign proteins and not with csDMARDs or tsDMARDs like JAK inhibitors. This group proposes that refractory RA be defined by resistance to multiple therapeutic drugs with different structures and mechanisms of action—in inefficacy of optimal dose methotrexate and at least two biologics with different mechanism of action. They suggest that multiple within-class bDMARD resistance (as with TNFi cycling) be excluded from the ambit of refractory RA and a patient failing MTX and one TNFi needs to fail another non-TNF before being labeled as refractory. The time period of 6 months incorporated in most guidelines for achieving LDA with treatment would translate into a period of at least 18–24 months for a patient to fail a minimum of two classes of bDMARDs. It is pertinent to point out that not incorporated in this working definition is the place of JAKi.

**How Common is Refractory RA?**

Biologics, contrary to the popular perception of many internists, do not work for all patients. As many as one-third of patients treated with TNF inhibitors exhibit inadequate response or intolerance. In general, the efficacy of biologics in patients failing methotrexate is given by the broad thumb rule of ACR-20/-50/-70 of 60/40/20%. That is, ACR 20 response is seen in 60% of such patients, ACR 50 response in 40% patients while ACR 70 response is seen in 20% patients. In patients failing anti-TNFs, the ACR-20/-50/-70 drop further to 50/25/12% respectively.

The prevalence estimates of refractory RA vary between 6% and 21% depending on threshold and study population. Obviously, referral centers would be expected to encounter more refractory patients. Risk factors for refractory RA include treatment delay, baseline disease activity and function, female gender, smoking, obesity, and lower socioeconomic status.

**How should Overdiagnosis of Refractory RA be Avoided?**

A label of refractory RA should be applied after careful consideration (Fig. 1). Overclassification and misclassification may result in inappropriate therapy escalation. Coexistence of fibromyalgia may lead to disproportionate increase in patient reported symptoms and distort disease assessment. Secondary damage and osteoarthritis can also lead to higher disease activity scores and apparent refractoriness.

**Treatment of Refractory RA**

The treatment of refractory RA revolves around the use of targeted treatments—bDMARDs or tsDMARDs. Patients failing one drug are switched to another agent. Switching to an alternate agent with same MOA (intra-class switching) has been called “cycling” and switching to agents with a different MOA has been termed “swapping.” These terms are by no means universally accepted. There is no consensus on sequence of switching. Physician familiarity, patient preference, and drug characteristics like availability, cost, safety, and efficacy are some of the factors to be considered. Of the ten bDMARDs available worldwide, six are available in India (Table 3). The tsDMARDs in RA are the JAK inhibitors. Two of the four JAKi are available for use in India (Table 4).
TABLE 3: Biologics available in India

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Target</th>
<th>Route of administration</th>
<th>Usual adult dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>TNF</td>
<td>Intravenous</td>
<td>In conjunction with methotrexate, 3 mg/kg at 0, 2, and 6 weeks, then every 8 weeks</td>
</tr>
<tr>
<td>Etanercept</td>
<td>TNF</td>
<td>Subcutaneous</td>
<td>50 mg weekly</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>TNF</td>
<td>Subcutaneous</td>
<td>40 mg every other week</td>
</tr>
<tr>
<td>Golimumab</td>
<td>TNF</td>
<td>Subcutaneous</td>
<td>50 mg once a month</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>IL-6R</td>
<td>Intravenous and subcutaneous</td>
<td>Intravenous: Recommended starting dose is 4 mg/kg every 4 weeks followed by an increase to 8 mg/kg every 4 weeks based on clinical response. Subcutaneous: 162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response</td>
</tr>
<tr>
<td>Rituximab</td>
<td>CD 20 on B cells</td>
<td>Intravenous</td>
<td>The dose for RA in combination with methotrexate is two-1,000 mg intravenous infusions separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks</td>
</tr>
</tbody>
</table>

IL-6R, interleukin 6 receptor; TNF, tumor necrosis factor
N.B.: Abatacept, Anakinra, Sarilumab, and Certolizumab are not available in India.

TABLE 4: Targeted synthetic (ts) DMARDs available in India

<table>
<thead>
<tr>
<th>Agent</th>
<th>JAKs targeted</th>
<th>Oral dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib</td>
<td>JAK1, JAK2, JAK3</td>
<td>5 mg BD</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>JAK1, JAK2</td>
<td>2–4 mg OD</td>
</tr>
</tbody>
</table>

JAK, Janus kinases
N.B.: Upadacitinib and Peficitinib are not available in India

Recommendations from professional bodies like APLAR and EULAR do not spell out any particular sequence to follow.\textsuperscript{2,11} It is to be pointed out that csDMARDs can be combined. However, combinations of biologics or JAKi or biologic-JAKi combination are not recommended for fear of intense immunosuppression (\textit{Flowchart 1}).
Refactory Rheumatoid Arthritis

CHAPTER 206

Refractory Rheumatoid Arthritis

References


Conclusion

Refractory RA represents an area of unmet need in the arena of rheumatology. The definition itself continues to evolve with the expansion of DMARD classes—from csDMARDs through bDMARDs to, now, tsDMARDs. Ensuring adherence to treatment and excluding the contribution of damage/degeneration to disease activity assessment are important to avoid misclassification as refractory RA. Biologics and tsDMARDs are used to treat refractory disease. In absence of biomarkers, the sequencing of bDMARDs and tsDMARDs at present is empirical. Hopefully, the advent of precision medicine in future would permit clinicians to move away from “generic” protocols to “individualized” protocols in the disease segment that is refractory RA!
Abstract

Rheumatoid arthritis is not an uncommon arthritis. There is overlap in the markers and clinical features. One should try to decipher the diagnosis with their markers and this will help in deciding treatment. By identifying the signs of flare ups and treatment failure we can plan treatment with algorithm.

Introduction

Rheumatoid arthritis marked by synovitis in small joints, acute phase reactants, and biomarkers. Sometimes biomarkers are absent but small joints and acute phase reactants are present diagnosis depend on clinical judgment and wait for others markers to evolve but if treated early, then long-term complications of join deformities and disabilities can be decreased. In presence of other biomarkers along with specific for Rheumatoid arthritis, subtle judgment will help in classifying disease syndrome. It is also pertinent to identify flare ups of disease and failure of treatment so that we can achieve remission. Finally treat to target will help in prolonging life.

Rheumatoid arthritis is one of the most common arthritis. Every clinician might have got an opportunity to treat it. They might have encountered some difficulties in the management, particularly in:

- Diagnosis
- Treatment

To diagnose rheumatoid arthritis when all clinical sings and markers are present is not a difficult task. Patients classically come with the complains of pain and early morning stiffness lasting for more than an hour and for more than 6 weeks with systemic symptoms or no systemic symptoms. There is an involvement of smaller joints in hand symmetrically, particularly involving proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints with positive squeeze sign and loss of guttering in between MCP joints, wrist, elbow, shoulder, knee, and feet with small joints. You can diagnose it easily if there is more than three symmetrical joints involvement in hand of PIP, MCP along acute phase reactants and autoimmune markers in the form of rheumatoid factor (RF) and anti-cyclic citrullinated (ACC) antibodies. When this is the situation, things are very easy. But the problem starts when:

- You have autoimmune markers but no clinical features or synovitis or joint pain.
- Clinical features of synovitis and evidence of symmetrical small joint arthritis with no autoimmune markers.

How to predict the diagnosis of rheumatoid arthritis in these two conditions.

Firstly, with autoimmune markers without evidence of synovitis:

- RF only
- Both RF and anti-cyclic citrullinated protein (ACCP) antibody

Secondly, with clinical features of synovitis and no autoimmune markers.
We have to take the account that genetic factors (e.g., the shared epitopes) are environmental factors (smoking and high body mass index) and RF isotypes particularly high-titer IgM-RF and IgA-RF presence will favor the future development of rheumatoid arthritis.

ACCP are of three types on the basis of method of antigen used anti-CCP1 (ELISA), anti-CCP2 (tested with synthetic peptides), anti-CCP3 (tested with synthetic peptides), of theses, presence of anti-CCP2 has more predictive value for the future development of RA.

With only presence of autoimmune markers, it takes 3–5 years to develop from the stage of autoimmunity to autoimmune disease. But it depends on:

- Levels of autoantibodies
- Number of ACCPs
- Presence of both ACCPs and RF
- Additional biomarkers such as cytokines and chemokines
- Other factors such as environmental exposures and symptoms

There different studies which show the predictive value have been discussed in the Table 1.

We need to develop an effective tools to measure the response of successful preventive interventions in preclinical RA (window of opportunity), when challenged with disease-modifying anti-rheumatic drug (DMARD) or other effective treatment in this window of opportunity.

Rituximab and other pharmacologic agents, including hydroxychloroquine, abatacept, and atorvastatin were tried in various trials for prevention in various trials without much success.

The best time to treat is when patients having arthralgia and synovitis. Treatment within first 3 months of onset of the disease can lead to long-term remission, the so-called window of opportunity period.

Now second situation is when there is a synovitis with typical joint involvement but no autoimmune markers, then how we can diagnose RA. We need:

- History of more than 6 weeks of morning stiffness, symmetric arthritis involving PIP, MCP joints, subcutaneous nodules, and the deformities characteristic of RA.

There are other disorders but having similar presentation but with presence of rashes, dry mouth and dry eyes, Raynaud's phenomenon, myositis, or nephritis, involvement typical organs and by various autoantibodies not seen in RA may clinch the diagnosis, for example. Systemic lupus erythematosus (SLE), Sjögren's syndrome, Dermatomyositis (DM), Sarcoidosis, Psoriatic arthritis, Overlap syndromes such as mixed connective tissue disease.

Some of inflammatory arthritis (IA) which do not fit in any of the classical syndrome, then we mark them as unclassified arthritis. Now even in these situations we can work up diagnosis in the favor of RA with anti-CCP presence, unconventional serologic findings (e.g., IgA type rheumatoid factor, pyridinoline), and MRI-proven early joint damage, synovial thickening, marrow edema, and erosions.

There are situations in which inflammatory arthritis is present with:

- RF with ANA (anti-nuclear antibodies) with erosions, the diagnosis goes the favors RA.
- Without erosions and clinical features suggestive of SLE or but with ANA and ACCP antibody clinch the diagnosis of rheumatoid arthritis.
- But patients having features of both RA and SLE with presence of RF and ANA will favor the diagnosis of overlap syndrome.

### TABLE 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Antigen Used</th>
<th>Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nielen et al (2004)</td>
<td>RF-IgM, anti-CCP2</td>
<td>PPV of up to 100% for RA diagnosis within 5 years</td>
</tr>
<tr>
<td>Deane et al. (2010)</td>
<td>RF isotypes, anti-CCP2</td>
<td>Anti-CCP and/or two or RF isotypes positive with &gt;96% PPV for RA compared to two control groups</td>
</tr>
<tr>
<td>Ramos-Remus et al. (2015)</td>
<td>RF, anti-CCP2</td>
<td>RF and anti-CCP positivity at baseline with PPV 64% for RA within 5 years; anti-CCP alone with PPV of 58%</td>
</tr>
<tr>
<td>Sokolove et al. (2012)</td>
<td>RF, ACPA array, variety of cytokines and chemokines</td>
<td>A set of ACPAs and cytokines was 58% sensitive and 87% specific for identifying a sample ≤2 years before diagnosis</td>
</tr>
</tbody>
</table>

ACPA, anti-citrullinated protein antibody; CCP, cyclic citrullinated protein/peptide; PPV, positive predictive value; RA, rheumatoid arthritis; RF, rheumatoid factor.
With RF, ANA, and Un RNP and IA, the diagnosis will go in favor of mixed connective tissue disease. Two of clinical variants of RA poses some difficulty. The first one is the presentation with monoarthritis. Mono arthritis with involvement a large joint, such as the wrist, knee, shoulder, hip, or ankle, may be the sole manifestation of RA, but how to predict RA in these patients. One should investigate the patients, for the presence of the RF and ACCP antibodies. If they are there, then wait for typical disease features to evolve. Usually it takes days to several weeks to develop polyarthritis from monoarthritis till then we should treat them as monoarthritis with NSAIDs and local steroid injection if required.

To rule out that monoarthritis of large joints are due to spondyloarthritis, MRI will help to find out more destructive change (synovial thickening, marrow edema, and erosions) in the patients with RA and but enthesopathy in the patients with spondyloarthropathy than in the patients with undifferentiated arthritis. Second one is the presentation with Palindromic rheumatism in this condition, episodes of joint inflammation sequentially affecting one to several joint areas for hours to days, with the symptom-free periods that may last from days to months. Patients with anti-CCP antibodies appear more likely to progress to definite RA later on. It has to be differentiated from the migratory arthritis.

So the key points for predicting RA we will need to focus on sex, age, morning stiffness, localization of symptoms, tender and swollen joint counts, C-reactive protein, rheumatoid factor positivity, and presence of ACCP antibodies. There are scoring systems to predict the development of RA.

We face some difficulties in treatment also. Firstly, in the choice of treatment, secondly detecting the failure of DMARD and lastly managing the flare ups. We usually start treating with NSAIDs (nonsteroidal anti-inflammatory drugs), steroid and CsDMARDs (conventional synthetic DMARD). But sometimes it does not give the desired results. Treat to the target is the rule of thumb.

Failure can be defined as:
- Not able to remission with the target achievement within 3–6 months of continuous use of DMARDS irrespective of nonbiologic (conventional synthetic [cs]), biologic (b), or targeted synthetic (ts) DMARD in maximally tolerated doses within the usual therapeutic range.
- Continued erosion despite patient on treatment even with no pain.
- Requirement of 5–7.5 mg prednisone or larger doses to maintain achievement after 3 months of DMARD use.
- Multiple courses of treatment with glucocorticoids for the treatment of recurrent disease flares in patients whose DMARD doses have been increased to the maximally tolerated.

Flares may be with:
- Single or few affected joints treated them with NSAIDs for few days and local steroid injection in joint if required.
- Widespread flares with multiple joints with need low doses of steroid.
- Severe flares, particularly those associated with systemic manifestations and life-threatening conditions, such as rheumatoid vasculitis will need intravenous pulse methylprednisolone in high doses with long use of steroid.
- Flaring frequently or severely will need escalation of doses of continued DMARD and/or addition of another DMARD of same group of different groups.

DMARDS are selected in step ladder approach:
- MTX (methotrexate)
- HCQ/SSZ (hydroxychloroquine/sulfasalazine)
- HCQ + SSZ + MTX, i.e., triple therapy
  Patients resistant to triple therapy can be treated with MTX plus leflunomide (LEF) please note that this may require closer monitoring (e.g., monthly with aminotransferase testing) for hepatotoxicity, given the increased risk of hepatotoxicity in some but not in the most studies, including reports of fatal liver failure.
- MTX + TNF blocker (tumor necrosis factor) ETN (Etanercept) or ADA (Adalimumab)
- Methotrexate plus Rituximab equivalent to TNF blocker combination
- Rituximab is effective alone in the patient intolerant with MTX
- MTX + tsDMARD (tofacitinib)
- LEF (leflunomide) alternative to MTX
- In pregnancy TNF blocker can be used alone
- LEF if there is moderate renal dysfunction/nontolerant to MTX
MTX + Abatacept
MTX + IL 6 inhibitors tocilizumab and sarilumab

Patient needs months and years of continued therapy for adequate response.

Downregulating the DMARDs only after 1 year of sustained response otherwise flare ups are very much common.

Some patients remain in remission on reduced doses but decision to discontinue treat remain debatable and controversial.

The best candidates for achieving a drug-free remission appear to be the patients who have a short duration of symptoms when treatment is started, are of the male sex, have an absence of RF and ACPAs, have received early intensive therapy, and have achieved a deep remission based upon composite scores of disease activity.

**Conclusion**

Autoimmune biomarker testing and clinical features allow us to rightly interpret the diagnosis. And knowing the failure, remission, and flare up sign and symptoms will lead to proper use of different demands in algorithm.

**Bibliography**

CHAPTER 208

Monoarthritis—A Clinical Dilemma to Internists

Arup Kumar Kundu, Abhishek Kundu

Abstract
The monoarthritis can either be acute or chronic, and may be either inflammatory or non-inflammatory. A detailed history and meticulous physical examination are essential in determining the etiology of arthritis. Diagnosis of monoarthritis is always a challenge to the internist. The common causes of acute monoarthritis are gout (crystal-induced arthritis), trauma, and infection, while that of chronic monoarthritis are osteoarthritis, tuberculous arthritis, gout, or spondyloarthropathy. So-called polyarticular diseases like systemic lupus erythematosus, rheumatoid arthritis may start as monoarthritis. If one investigation has to be done, it is synovial fluid examination, while synovial biopsy specimen is often examined for etiological agents in Lyme disease, gonococci, tuberculosis, or chlamydia infection. Light microscopy may identify gout crystals, but polarized microscopy is always preferred. Review of systemic diseases like sarcoidosis, malignancy, etc. is important because they may be complicated by monoarthritis.

Introduction
Monoarthritis is defined as inflammation of one joint at a time, while acute monoarthritis is acute inflammation of a single previously healthy joint, typically developing within a few days. Chronic monoarthritis is the inflammatory arthritis of a single joint that persists for more than 6 weeks. Acute monoarthritis may be the initial manifestation of many of the rheumatological disorders or systemic connective tissue diseases. The most common causes of acute monoarthritis are crystal arthropathy (i.e., gout and pseudogout), trauma, and infection. The patient of monoarthritis should undergo careful and meticulous history, rational physical examination, and selected laboratory tests. Acute monoarthritis (red-hot joint) represents a rheumatologic emergency and requires rapid assessment, diagnosis, and aggressive treatment, since an untreated septic arthritis may lead to irreversible joint damage and resultant disability. In spite of the intensive investigations, at times, no clear diagnosis can be made. Complete blood count, bleeding and clotting time, ESR, C-reactive protein (CRP), serum uric acid, rheumatoid factor and antinuclear factor, urine analysis, and blood or urine culture should be performed, as and when necessary. Blood culture should be done if clinical suspicion of septic arthritis is very high. Many a time, examination of joint fluid is essential in making a definitive diagnosis. Leukocyte counts may vary widely in septic and sterile synovial fluids, and should be interpreted cautiously in an open mind. The joints, such as hip or sacroiliac joints, are difficult to aspirate and very often computed tomography or ultrasound-guided arthrocentesis helps to draw synovial fluid from these types of deep-seated joints. When an infection is suspected, culture and Gram staining of the synovial fluid should be performed and antibiotics should be started empirically. Light microscopy may identify gout crystals, but polarized microscopy is always preferred. If, however, the diagnosis is yet to be reached, radiographic studies (such as technetium bone scan,
computed tomographic scanning or magnetic resonance imaging) are performed in selected cases (such as internal derangement or osteonecrosis), and even, invasive procedures such as arthroscopy and synovial biopsy may be necessary to clinch the final diagnosis in undiagnosed chronic monoarthritis. The other systems should be evaluated because, many a time, thalassemia, sarcoidosis, sickle cell anemia, or hemophilia may be a cause for monoarthritis.

**Monoarthritis: An Overview**

Monoarthritis represents a diagnostic challenge to every physician. The doctor first decides the anatomical basis of pain (i.e., articular vs. non-articular). Joint pain can be the result of abnormalities in the joint itself, adjacent bone, surrounding ligaments, tendons, bursa, or soft tissues. Articular structures consist of synovium, synovial fluid, articular cartilage, joint capsule and juxta-articular bone. Non-articular (periarticular) structures include ligaments, bone, tendons, bursa, muscle, fascia, nerve, and overlying skin. "Arthritis" results in stiffness, reduced range of motion, and pain of the involved joint during normal use, which is most noticeable in the morning, improves with motion, and may be associated with systemic symptoms (i.e., malaise or fever). Joint pain due to mechanical factors (non-articular) usually improves with rest, deteriorates with activities and is not associated with systemic symptoms. In differential diagnosis (D/D) of musculoskeletal pain diffuse bone diseases like multiple myeloma, metabolic bone disease or multifocal osteomyelitis should be considered.

Possible causes of acute and chronic monoarthritis have been elaborated in Table 1. Arthritis may be monoarthritis (single joint), oligo- or pauciarticular (2–4 joints) or polyarticular (5+ joints).

**TABLE 1** Etiology of monoarthritis

<table>
<thead>
<tr>
<th>Common causes</th>
<th>Less frequent causes</th>
<th>Rare causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>Malignancy of bone</td>
<td>Hypertrophic pulmonary osteoarthropathy (developing from bronchogenic carcinoma)</td>
</tr>
<tr>
<td>Crystals—monosodium urate (MSU), calcium pyrophosphate dehydrate (CPPD), hydroxyapatite, calcium oxalate</td>
<td>Hemoglobinopathies (i.e., sickle cell anemia)</td>
<td>Foreign body (e.g., plant thorn)</td>
</tr>
<tr>
<td>Septic arthritis (non-gonococcal, gonococcal)</td>
<td>Enteropathic arthritis (e.g., Crohn’s disease, ulcerative colitis)</td>
<td>Pigmented villonodular synovitis</td>
</tr>
<tr>
<td>Hemarthrosis (trauma and/or coagulation disorder)</td>
<td>Sarcoidosis</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Avascular necrosis of bone (i.e., osteonecrosis)</td>
<td>Loose bodies within joint</td>
<td>Lyme disease</td>
</tr>
<tr>
<td>Internal derangement (e.g., meniscus tear, cartilage debris)</td>
<td>Infections—mycobacteria, fungi</td>
<td>Familial Mediterranean fever</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>Leukemia</td>
<td>Relapsing polychondritis</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>Rheumatoid arthritis (RA—palindromic), reactive arthritis (ReA), psoriatic arthropathy (PsA), juvenile idiopathic arthritis (JIA)</td>
<td>Charcot joint</td>
</tr>
<tr>
<td>Overuse (e.g., in a pre-existing osteoarthritic joint)</td>
<td>Vasculitis</td>
<td>Behçet’s syndrome</td>
</tr>
<tr>
<td>Monoarticular flare of oligoarthritides or polyarthritis</td>
<td></td>
<td>Synovial chondromatosis/sarcoma/synovial metastasis</td>
</tr>
</tbody>
</table>
joints) and polyarthritis (≥5 joints). Monoarthritis can either be acute (duration <6 weeks) or chronic (duration >6 weeks), and may be either inflammatory or non-inflammatory (Table 2).²,³

### Approach to Evaluation of Monoarthritis

The first and most important steps in evaluation are thorough history taking. Onset of symptoms, history of fever, recent travel, IV drug or alcohol abuse, sexual exposure, tick or insect bite, diarrhea, urinary tract infection, trauma, gardening (e.g., plant thorn synovitis), or pre-existing systemic disease should be enquired. History of drug therapy (e.g., diuretics in gout), skin rash, oral or genital ulcers, and prolonged bleeding should be taken into account (Table 3). Next task is to start thorough physical examination where a physician has to differentiate articular from non-articular disease (see previous paragraph). Deep-seated joints like hip and sacroiliac joints are difficult to evaluate. Consider the D/D of single “red-hot joint” (Table 4).

Clue for initial clinical observation (ideal examples):
- Middle-aged male with red, hot, tender, and swollen 1st metatarsophalangeal joint points toward gout.
- Elderly diabetic lady having knee replacement 1 year back where the knee is presently acutely swollen, hot, tender with high pyrexia, and toxicity indicates septic arthritis.
- Young male with acute knee pain, plus history of neck and back pain will have a probable diagnosis of ankylosing spondylitis (SpA).
- Young male with acute knee pain, plus history of neck and back pain will have a probable diagnosis of ankylosing spondylitis (SpA).

### TABLE 2 Working classification according to onset and duration²,³

<table>
<thead>
<tr>
<th>Acute (duration &lt;6 weeks)</th>
<th>Chronic (duration &gt;6 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Infection (bacterial, mycobacterial, fungal, or viral; Lyme disease)</td>
<td>- Infection (tuberculosis, brucellosis, fungal)</td>
</tr>
<tr>
<td>- Crystals (MSU, CPPD, calcium hydroxyapatite, calcium oxalate)</td>
<td>- Crystals (MSU, CPPD, etc.)</td>
</tr>
<tr>
<td>- Trauma (fracture or internal derangement)</td>
<td>- Osteoarthritis (commonly knee joint)</td>
</tr>
<tr>
<td>- Monoarticular presentation of a polyarticular disease (i.e., immunoinflammatory—RA, SpA, PsA, IBD, or SLE)</td>
<td>- Sarcoïdosis (e.g., ankle joint)</td>
</tr>
<tr>
<td>- Osteoarthritis (knee, hip, or 1st MCP)</td>
<td>- Seronegative SpA and chronic ReA</td>
</tr>
<tr>
<td>- Hemarthrosis (trauma, coagulation abnormality)</td>
<td>- Pigmented villonodular synovitis (PVNS)</td>
</tr>
<tr>
<td>- Ischemic (vascular) necrosis—of hip from SLE or corticosteroid therapy</td>
<td>- Synovial chondromatosis/sarcoma</td>
</tr>
<tr>
<td>- Tumor (metastasis, PVNS)</td>
<td>- Foreign body (plant thorn) synovitis</td>
</tr>
<tr>
<td>- Foreign body synovitis (wood fragments, plant thorn)</td>
<td>- Charcot (neuropathic) joint (e.g., leprosy, syringomyelia)</td>
</tr>
<tr>
<td>- Systemic diseases presenting as monoarthritis (e.g., acromegaly producing pseudogout)</td>
<td>- Monoarticular presentation of a polyarticular disease (i.e., RA, SpA, PsA)</td>
</tr>
</tbody>
</table>

Summary of working classification:
Acute monoarthritis—Septic, crystals, traumatic, SpA (especially, ReA)
Chronic monoarthritis—Osteoarthritis, crystals, SpA (especially chronic ReA), tuberculous

IBD, inflammatory bowel disease; MCP, metacarpophalangeal; PsA, psoriatic arthropathy; RA, rheumatoid arthritis; ReA, reactive arthritis; SLE, systemic lupus erythematosus; SpA, spondyloarthropathy
TABLE 3  Clinical clues in the history and physical examination

<table>
<thead>
<tr>
<th>History and clinical findings</th>
<th>Probable diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden onset of pain developing within seconds or minutes</td>
<td>Trauma, fracture, internal derangement</td>
</tr>
<tr>
<td>Onset of pain arising over several hours or within days</td>
<td>Infection, crystal arthropathy, any inflammatory arthritis</td>
</tr>
<tr>
<td>Onset of pain developing over days to weeks</td>
<td>Indolent infection, osteoarthritis, infiltrative disease, tumor (synovium/bone)</td>
</tr>
<tr>
<td>Young adult with history of promiscuous sex and migratory arthritis</td>
<td>Gonococcal arthritis</td>
</tr>
<tr>
<td>History of diabetes mellitus, immunosuppression, bacterial endocarditis, or IV drug abusers</td>
<td>Septic arthritis</td>
</tr>
<tr>
<td>Previous history of acute attack in the joint with spontaneous resolution</td>
<td>Gout, any inflammatory arthritis</td>
</tr>
<tr>
<td>History of sustained bleeding (coagulopathy) or use of anticoagulants</td>
<td>Hemarthrosis</td>
</tr>
<tr>
<td>Positive family history</td>
<td>Gout, IBD-induced spondyloarthropathy, psoriasis, ankylosing spondylitis, osteoarthritis</td>
</tr>
<tr>
<td>Prolonged use of corticosteroid in the recent past</td>
<td>Infection, avascular necrosis</td>
</tr>
<tr>
<td>Urethritis (chlamydiae), conjunctivitis, skin or penile rash, diarrhea (campylobacter, salmonella, shigella)</td>
<td>Reactive arthritis (ReA)</td>
</tr>
<tr>
<td>Arthritis precipitated after binge alcohol intake or consumption of diuretics</td>
<td>Gout</td>
</tr>
<tr>
<td>Low back pain, uveitis (red eye), heel pain, or Achilles tendonitis</td>
<td>Ankylosing spondylitis</td>
</tr>
<tr>
<td>Hilar adenopathy, erythema nodosum (Lofgren syndrome)</td>
<td>Sarcoidosis</td>
</tr>
</tbody>
</table>

Bedside clinics:
- Oral ulcers
- Pyrexia
- Lymphadenopathy
- Tophi over olecranon process, or helix
- Erythematous rash in face
- Bronzing (darkening) of skin
- Pyoderma gangrenosum
- Erythema nodosum
- Psoriatic skin patches or pitting nails
- Circinate balanitis or keratoderma blenorrhagicum
- Behçet’s disease, SLE, ReA
- Infection, crystals, immunoinflammatory
- Tuberculosis, malignancy
- Gout
- SLE (butterfly-like), lupus pernio (sarcoidosis)
- Pseudogout (hemochromatosis)
- IBD, RA
- IBD, SLE, sarcoidosis, tuberculosis
- Psoriatic arthritis
- ReA

TABLE 4  Acute monoarthritis presenting as ‘red-hot joint’

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Bacterial (Staphylococci, Streptococci, Gonococci, gram-negative organisms), viral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystal-induced</td>
<td>Gout, pseudogout (i.e., from hemochromatosis, acromegaly, hypoparathyroidism)</td>
</tr>
<tr>
<td>Acute exacerbation of:</td>
<td>RA, ReA, PsA, palindromic rheumatism</td>
</tr>
</tbody>
</table>

Pitfalls and Reality in Monoarthritis (Table 5)

Management
Management of acute monoarthritis depends on the actual diagnosis though the general principles of management include rest to the joint, application of ice, and physiotherapy to help maintain range of motion in joints and minimize subsequent muscle atrophy. Specific therapy includes antibacterial agents for septic arthritis, non-steroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular corticosteroid injections for non-infectious inflammatory monoarthritis; arthroscopy is performed for internal derangement. Presence of infection

...serum uric acid, and rheumatoid factor. Radiology is not much helpful except in saccroiliitis, osteoarthritis, and chondrocalcinosis (e.g., pseudogout). MRI may be helpful in deep-seated arthritis.
should always be ruled out before giving intra-articular corticosteroid injection. Acute gout should be treated with colchicine, NSAIDs, or prednisolone. Joint aspiration is necessary in hemarthrosis. Osteoarthritis patients are advised to save their cartilage by practical demonstration, and treated with intra-articular corticosteroid and/or hyaluron injection. Pain in reactive arthritis is relieved by NSAIDs and ultimately the patients are advised to take disease-modifying anti-rheumatic drugs (DMARDs).

If the clinical suspicion of septic arthritis is very strong, empiric antibiotic therapy should be started, pending the reports of synovial fluid analysis. Modifications of antibiotics and its dosage may be done as soon as Gram staining and culture reports of synovial fluid are available. Septic arthritis should be treated in a hospital under the supervision of an orthopedic surgeon. Many a time, surgical drainage of a septic arthritis is required.

**Practical Recommendations for Acute Monoarthritis**

- Acute monoarthritis is a medical emergency. With a short history of red-hot swollen joint, one should always suspect infection and unless otherwise indicated, it should be treated as septic arthritis. Other D/D are acute gout, trauma, and acute onset of inflammatory polyarthritis.
  - The most significant point of clinical examination is to differentiate true synovitis (i.e., arthritis) from periarticular disease (e.g., cellulitis, bursitis, etc.).
  - Septic arthritis can destroy a joint very rapidly, if not treated promptly. Septic arthritis is often superimposed on gout or pseudogout. Gonococcal arthritis is commonly a disease of sexually active young women.
  - RA, ReA, IBD-associated arthritis, SLE, PsA, Behçet’s disease can begin as acute monoarthritis, while systemic diseases like sarcoidosis, sickle cell anemia, or hemophilia may be complicated by monoarthritis. Tuberculosis and other indolent infections should be considered in chronic monoarthritis, and synovial biopsy may be needed to pin-point the diagnosis.
  - The synovial fluid should be aspirated and sent for Gram staining and cultures (apart from total analysis) in acute and chronic monoarthritis. Synovial fluid analysis is the most important investigation.
  - Absence of leukocytosis/high ESR/high CRP, negative Gram stain, or negative synovial fluid cultures does not exclude infection.

---

**TABLE 5** Pitfalls versus reality in diagnosing monoarthritis

<table>
<thead>
<tr>
<th>Pitfalls</th>
<th>Reality</th>
</tr>
</thead>
<tbody>
<tr>
<td>A normal serum uric acid level excludes gout</td>
<td>Serum uric acid may be normal or low up to 30% cases of gout as stress-induced liberation of ACTH and TNF-α may act uricosuric. Moreover, there may be unrelated asymptomatic hyperuricemia associated with other monoarticular arthritis</td>
</tr>
<tr>
<td>Presence of fever distinguishes infective from non-infective arthritis</td>
<td>Presence of fever is not a reliable indicator of septic arthritis, and moreover acute attack of gout or pseudogout may be associated with pyrexia. Similarly, absence of leukocytosis, raised ESR, raised CRP, or absence of organisms does not exclude septic arthritis</td>
</tr>
<tr>
<td>Presence of crystals (MSU or CPPD) in the joint fluid rules out infection</td>
<td>Crystal may be present in septic arthritis</td>
</tr>
<tr>
<td>The problem is always in the ‘joint’ as the patient complains of joint pain</td>
<td>Many a time, soft tissue rheumatism due to adjacent soft tissue inflammation (such as olecranon bursitis of the elbow) may be the source of pain</td>
</tr>
<tr>
<td>Diseases manifested as polyarthritis cannot have monoarthritis-like presentation</td>
<td>Monoarticular flare of rheumatoid arthritis or reactive arthritis is not uncommon</td>
</tr>
<tr>
<td>A negative Gram staining and culture of synovial fluid virtually excludes infection</td>
<td>Results of culture may be negative in early infection, and thus culture of blood/urine should be performed repeatedly in strong clinical suspicion of infection</td>
</tr>
<tr>
<td>In synovial fluid analysis, presence of WBC &gt;2,000/mm³ clinches the diagnosis of septic arthritis</td>
<td>Synovial fluid WBC &gt;2,000/mm³ is very often found in RA, SpA, SLE, or gout</td>
</tr>
</tbody>
</table>
In gout, synovial fluid samples must be sent for polarized microscopy for demonstration of intracellular MSU crystals as serum uric acid may be normal in acute attack of gout; in its absence, ordinary microscopy often gives a clue for crystals.

Plain X-ray of the affected joint is usually of no benefit.

In septic arthritis, start relevant antibiotics as early as possible pending culture reports. Usual pathogens are *Staphylococcus aureus* or streptococci but Gram-negative organisms are commoner in the elderly and immunocompromised patients. Conventionally, IV antibiotics are given for 2 weeks, followed by oral antibiotics for 4 weeks or more till local/systemic manifestations resolve and acute phase reactants (e.g., CRP) return to normal.

Septic arthritis should be treated by orthopedic surgeon, crystal arthropathy, and inflammatory arthritis by rheumatologist, and osteoarthritis by orthopedic surgeon and physiatrist jointly.

**Conclusion**

Acute monoarthritis is a rheumatologic emergency and demands prompt diagnosis. So far as diagnosis and treatment of chronic monoarthritis are concerned, it needs patience, sound clinical background, and experience. Prompt diagnosis of joint infection is crucial as it rapidly results in joint destruction. Before putting the needle within a joint to inject corticosteroid, it is the duty of orthopedic surgeon or rheumatologist to exclude infective arthritis. The diagnostic and therapeutic dilemma in monoarticular arthropathy can be solved easily if the attending doctor examines the patient meticulously, and analyze the clinical findings and investigation reports logically.

**References**

CHAPTER 209

Oral Targeted Treatments in RA—Update 2021

Ramakrishna Rao Uppuluri, Sripurna Deepti Challa

Abstract

The current concept in the management of rheumatoid arthritis (RA) and other immune-inflammatory arthritis is “treat to target”, the target being low disease activity or remission. The standard of care in RA involves pharmacotherapy initiating conventional synthetic disease modifying anti-rheumatoid drugs. However, some patients do not respond to the conventional therapy. Advanced target therapy for RA involves biologic agents or oral small molecules. JAK inhibitors, a form of oral targeted treatment, are convenient, orally administered which do not produce drug antibodies. Robust clinical trials demonstrated their efficacy and safety.

Introduction

Among the inflammatory polyarthritis, rheumatoid arthritis (RA) is the most common. Over the past few decades, significant advances were made in understanding the pathogenesis of RA. The role of several important proinflammatory cytokines, such as tumor necrosis factors (TNF), interleukins (e.g., IL-6), and cell-associated targets (e.g., CD20) have been validated by the use of targeted biologic therapies in last two decades. Standard of care in RA involves initiation of the treatment with conventional synthetic disease modifying anti-rheumatoid drugs (csDMARDs) such as methotrexate (MTX). Biologic therapies (bDMARDs) have led to further reduction of the signs and symptoms of RA resulting in low disease activity (LDA) or remission of the disease. However, they have limitations—they have to be given parenterally and stored at lower temperatures. They can induce immunogenicity developing tolerance. Small molecules with low molecular mass that inhibit intracellular inflammatory signaling pathways are developed during the last decade. They are an important alternative to biologics for RA. These are called oral targeting treatments of RA.

Advances in the Treatment of RA

In the treatment of RA, csDMARDs occupy a central role (Flowchart 1). MTX is still a baseline therapy unless contraindicated. Most of the rheumatologists use combination therapy with csDMARDs.1

However, significant number of the patients of RA do continue to progress with erosive arthritis. Biologic era in the past few years had seen remarkable advancement in the therapy of RA. In view of persistent unmet needs in the management of RA, oral targeted therapy inhibiting intracellular signaling pathways is developed in the last decade (Fig. 1).2

Oral Targeted Therapy: Janus Kinase Inhibitors

Intracellular signaling pathways involved in signal transduction from the cell surface to the nucleus after ligand receptor binding have been identified. Small molecular therapies target these intracellular pathways. Protein kinases that phosphorylate intracellular proteins are major players in signal transduction. Tyrosine kinases,
Janus kinases (JAKs), and Serine kinases are some of the protein kinases (Flowchart 2).

Receptor polymerization and activation of associated JAKs occur once the cytokine binds to its cell surface receptor. JAKs, named after the two-faced Roman God Janus, consist of four types—JAK1, JAK2, JAK3, and TYK2. Phosphorylation of the receptors activated by JAKs dock the STATs (Signal Transduction Activator Transcription) (Figs. 2A and B). They dimerize, translocate to the nucleus, and activate new gene transcription generating further cytokines (Figs. 2C and D).³

JAK inhibitors (Jakinibs) have been successfully developed as oral targeted therapy in RA. Autophosphorylation and further activation of JAKs is inhibited by Jakinibs, for example, Tofacitinib. JAKs cannot phosphorylate the receptors and cannot dock the STATs. Phosphorylation of STATs, dimerization, and translocation are inhibited. Hence, gene transcription and further
production of cytokines do not take place (Fig. 3). There are seven STATs: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6. Different cytokines have the ability to preferentially recruit different STATs by virtue of selective binding to cytokine receptors. The JAK/STAT pathways exert their function through type I and type II receptors. Type I receptors are used by several interleukins (ILs), colony-stimulating factors, and hormones, while type II receptors are used by interferons (IFNs) and IL-10 related cytokines (Fig. 4).

Tofacitinib, one of the early Jakinibs, was approved in the USA in 2012 for the treatment of moderately severe RA not responding to conventional therapy and was approved in India by 2016. Baricitinib, another Jakinib, is also approved in India for the treatment of RA more than a year ago. Upadacitinib and Filgotinib are other Jakinibs yet to enter Indian market. All these molecules have undergone robust clinical trials for efficacy in RA (Tables 1 and 2). Randomized controlled trials (RCT) and long-term extension (LTE) studies have shown that Jakinibs are as efficacious as biologics. Safety profiles of these Jakinibs have also been carefully monitored long term. Tofacitinib in Indian patients with RA had confirmed its efficacy and safety by a post hoc analysis in Phase 3 and LTE studies over 7 years.

The Place of Jakinibs in Contemporary RA Management

Tofacitinib and baricitinib are currently available Jakinibs for the treatment of patients with moderately severe RA.
not responding to conventional DMARDs. Tofacitinib targets mainly JAK1, JAK3 and Baricitinib JAK1, JAK2. Tofacitinib is also approved in other disorders such as psoriatic arthritis (PsA) and ulcerative colitis (UC). Many more Jakinibs are in the process of randomized clinical trials⁹ (Table 3).

**Drug Target Indications**

American College of Rheumatology (ACR) guidelines and European League against Rheumatism (EULAR) recommendations for the management of RA advise use of MTX to begin with.¹⁰,¹¹ However, only a third of patients with early RA benefit from MTX monotherapy in controlling disease activity, improving patient reported outcome measures (PROMs) and slowing radiographic progression.¹² The ACR guidelines recommend combination of csDMARDs or
**TABLE 1**  
Tofacitinib in RA—phase 3 studies: overview

<table>
<thead>
<tr>
<th>Study(N)</th>
<th>DMARD-IR</th>
<th>MTX-IR</th>
<th>TNFi-IR</th>
<th>MTX naïve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORAL solo (N=610)</td>
<td>ORAL Sync (N=792)</td>
<td>ORAL Standard (N=717)</td>
<td>ORAL Scan (N=797)</td>
</tr>
<tr>
<td>Duration months</td>
<td>6 12</td>
<td>12 24</td>
<td>24</td>
<td>6 24</td>
</tr>
<tr>
<td>Background</td>
<td>None</td>
<td>Nonbiologic DMARDs</td>
<td>MTX</td>
<td>MTX</td>
</tr>
<tr>
<td>Feature</td>
<td>Monotherapy</td>
<td>Background cDMARDs</td>
<td>Active control (ADA)</td>
<td>Radiographic outcomes</td>
</tr>
</tbody>
</table>

ACR, American College of Rheumatology; ADA, adalimumab; BARI, baricitinib; cDMARDs, conventional disease modifying antirheumatic drugs; DAS, disease activity score; HAQ-DI, health assessment questionnaire-disability index; IR, inadequate responders; mTSS, modified total sharp score; MTX, methotrexate; PBO, placebo; RA, rheumatoid arthritis; TNFi, tumor necrosis factor inhibitor.

**TABLE 2**  
Baricitinib in RA—phase 3 clinical trials overview

<table>
<thead>
<tr>
<th>DMARD naïve</th>
<th>cDMARD-IR</th>
<th>Biologic IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA BEGIN MTX-naïve</td>
<td>RA BEAM MTX-IR</td>
<td>RA BEACON TNFi-IR</td>
</tr>
<tr>
<td>MTX</td>
<td>PBO</td>
<td>PBO</td>
</tr>
<tr>
<td>BARI 4 mg mono</td>
<td>BARI 4 mg + MTX</td>
<td>BARI 2 mg</td>
</tr>
<tr>
<td>BARI 4 mg + MTX</td>
<td>ADA 40 mg + MTX</td>
<td>BARI 4 mg</td>
</tr>
<tr>
<td>52 weeks</td>
<td>52 weeks</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

RA BEYOND (long-term extension)

ADA, adalimumab; BARI, baricitinib; cDMARDs, conventional disease modifying antirheumatic drugs; IR, inadequate responders; MTX, methotrexate; PBO, placebo; RA, rheumatoid arthritis; TNFi, tumor necrosis factor inhibitor.

**TABLE 3**  
Some JAKINIBS—their targets and indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib (Xeljanz)</td>
<td>JAK1, JAK3, JAK2</td>
<td>RA (approved in India also), PsA, UC</td>
</tr>
<tr>
<td>Baricitinib (Olumiant)</td>
<td>JAK1, JAK2</td>
<td>RA (approved in India also)</td>
</tr>
<tr>
<td>Peficitinib (Smyraf)</td>
<td>JAK1,2,3, TYK2</td>
<td>RA (approved in Japan)</td>
</tr>
<tr>
<td>Upadacitinib (Rinvoq)</td>
<td>JAK1</td>
<td>RA (approved in USA)</td>
</tr>
<tr>
<td>Filgotinib</td>
<td>JAK1</td>
<td>RA (completing clinical trials)</td>
</tr>
<tr>
<td>Decernotinib</td>
<td>JAK3</td>
<td>RA (continuing clinical trials)</td>
</tr>
<tr>
<td>BMS-986165</td>
<td>TYK2</td>
<td>PsA (started clinical trials)</td>
</tr>
</tbody>
</table>
addition of a bDMARD or a Jakinib, when the patients fail to achieve a satisfactory response to MTX monotherapy and a short period of glucocorticoids. Jakinibs with or without MTX are also considered in bDMARD inadequate responders. EULAR recommendations also advise similar management for RA, especially with poor prognostic factors such as high titers of RF/ACPA (anti-cyclic citrullinated protein antibodies), high disease activity, early joint damage and/or failure of two or more csDMARDs (Fig. 5).

Real world evidence for safety and efficacy of Jakinibs is also necessary to bridge the gap between RCTs and rheumatology clinics. Usually there is little difference in the screening and monitoring of infections between Jakinibs and biologics. Increased risk of Herpes zoster may be common to all Jakinibs. In real world practice,
TABLE 4 Some of the ongoing clinical trials with JAKINIBS other than RA

- Juvenile arthritis
- Ankylosing spondylitis
- Psoriatic Arthritis
- Crohn’s disease
- Ulcerative colitis
- Uveitis
- Sjogren’s syndrome
- Psoriasis
- Alopecia areata
- Atopic dermatitis
- Scleroderma
- Lupus
- Vasculitis

accumulation of cases to evaluate risks of relatively rare serious adverse events (SAEs) is needed. Some of the SAEs are thromboembolic events, gastrointestinal (GI) perforation, and interstitial lung disease. Pharmacovigilance activity is required to establish the efficacy and safety of Jakinibs in patients with RA and other rheumatic diseases (Table 4).

Advantages of Jakinibs

Jakinibs are orally administered small molecules unlike biologics, which are large proteins and given only by subcutaneous or intravenous. Jakinibs act fast showing their benefits within 1–2 weeks. Small molecules can be synthesized easily, carried easily, and do not require cold chain. They do not have immunogenicity seen in some biologics; hence do not generate drug antibodies. Since their half-life is short for a few hours, they can be stopped in situation where infection is suspected with a rapid reversal of drug-related side effects. Blockade of a wide spectrum of cytokines may cover many inflammatory pathways. Tofacitinib and Baricitinib with background MTX proved to be non inferior and superior respectively over standard of care biologic Adalimumab in active RA.15 PROMs, such as pain, function and fatigue are improved very well with Jakinibs.16,17

Side Effects of Jakinibs

Infections

Usage of Jakinibs may increase serious and opportunistic infections. However, the rate of infections is not more than biologics except Herpes zoster.19 The risk of reactivation of varicella zoster virus is increased by the use of Jakinibs with the combination of steroids and MTX. Before starting therapy with Jakinibs, vaccination against Herpes zoster is considered. Treatment with Jakinibs can cause anemia and decreased cell counts including lymphocytes, neutrophils, and platelets.20 There is no particular association of these changes with serious infections or malignancy.

Tuberculosis

RA itself can increase the susceptibility to tuberculosis (TB). Biologics especially the TNF inhibitors increase the risk of TB, mostly in an endemic area. The incidence is less with Jakinibs. Among 5,671 subjects enrolled in Phase 2 and 3 and LTE studies of Tofacitinib, 26 cases of TB were reported. The median time between the start of Tofacitinib and diagnosis of TB was 64 weeks (15–161). Extrapulmonary infection occurred in fifteen (58%) cases. Most cases (20/26, 77%) were reported in those taking Tofacitinib 10 mg twice a day. However, globally Tofacitinib dosage is only 5 mg BID in RA. TB rate with Jakinibs was also associated with endemicity.21

Thromboembolic Events

Possibility of increased risk of thromboembolic events is noted with the use of Baricitinib. RA itself has a tendency to develop the risk of deep venous thrombosis and pulmonary embolism. Relating this complication to the action of a specific or a group of cytokines is difficult. JAK2 inhibition disturbs thrombopoietin signaling and platelet homeostasis, but its relation to thrombosis is ill-defined.22

Malignancy

Patients with RA have an increased incidence of malignancy including lymphoma. The rate of cancer in patients on Jakinibs is similar to those on biologics23 (Table 5).

Other Problems

Jakinibs are associated with an increase in total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) particles. Jakinibs may limit vascular damage by decreasing inflammation in spite of increased cholesterol.24 Minimal increases in creatine phosphokinase levels are observed without overt muscle disease. The use of Jakinibs may be associated with increased liver enzymes and GI perforation. Jakinibs are
contraindicated at the time of pregnancy. Women of childbearing age should use effective contraception while on treatment. During breastfeeding, Jakinibs should not be used.

**Conclusion**

- JAK inhibitors are the latest addition of the treatment of RA in the last decade.
- They act by blocking intracellular JAK/STAT signaling pathways inhibiting the production of inflammatory cytokines.
- They are rapidly acting, oral targeting anti-rheumatoid drugs with convenience.
- They showed sustained efficacy and established safety by robust clinical drug trials and real world experience.
- Recommended as a second line therapy for csDMARDs inadequate responders or Biologic inadequate responders by several guidelines.

**References**


**TABLE 5** Incidence rates of adverse events of special interest of JAKINIBS in RA

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Tofacitinib</th>
<th>Baricitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious infection</td>
<td>2.7 (2.5, 3.0)</td>
<td>2.9 (2.5, 3.4)</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>3.9 (3.6, 4.2)</td>
<td>3.2 (2.8, 3.7)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0.2 (0.1, 0.3)</td>
<td>0.15 (0.07, 0.27)</td>
</tr>
<tr>
<td>Malignancy excluding NMSC</td>
<td>0.9 (0.8, 1.0)</td>
<td>0.8 (0.6, 1.0)</td>
</tr>
<tr>
<td>NMSC</td>
<td>0.6 (0.5, 0.7)</td>
<td>0.4 (0.2, 0.5)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0.1 (0.1, 0.2)</td>
<td>0.09 (0.03, 0.19)</td>
</tr>
<tr>
<td>MACE</td>
<td>0.58 (0.39, 0.88)</td>
<td>0.5 (0.4, 0.7)</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>DVT: 0 in PBO-controlled cohort and 0.1 (0, 0.3) in dose-comparison cohort PE: 0 in PBO-controlled cohort and 0.1 (0, 0.4) for 5 mg bid</td>
<td>DVT/PE: 0.5 (0.3, 0.7)</td>
</tr>
<tr>
<td>GI perforation</td>
<td>0.11 (0.07, 0.17)a</td>
<td>0.05 (0.01, 0.13)</td>
</tr>
</tbody>
</table>

Incidence rates (95% CIs) in RA patients treated with each JAK inhibitor were shown.

DVT, deep vein thrombosis; GI, gastrointestinal; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PBO, placebo; PE, pulmonary embolism.
CHAPTER 210

Biosimilars: Bane or Boon for India

Durga Prasanna Misra, Pallavi Patro, Vikas Agarwal

Abstract
Biosimilars are structural analogues of innovator biological drugs which have undergone rigorous development and testing. In this chapter, we overview definitions of biosimilars, biomimics, and biocopies; review regulatory processes for biosimilar approval; and discuss the concepts of extrapolation, switch, substitution, re-switch, and nocebo effect as assess perspectives for biosimilar use (including cost) from an Indian perspective.

Introduction
Better understanding of pathophysiological process driving disease has given rise to targeted therapies for the treatment of these diseases. Biologic drugs are drugs administered parenterally, which target specific molecular pathways resulting in disease phenotypes. Biologic drugs are now used in many medical specialties such as Rheumatology, Hematology, Oncology, and Nephrology.1-3

The classical example of a biologic drug that has revolutionized patient management in drugs targeting the proinflammatory cytokine tumor necrosis factor alpha (TNF-α) in disease settings like rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Such anti-TNF therapies have become frontline agents for the management of these lifelong inflammatory diseases, and markedly improved disease control in those refractory to conventional disease-modifying antirheumatic drugs. However, despite their use being described in RA and AS since the late 1990s, anti-TNF agents remained out of reach for a majority of the Indian populace until recently, in no small part due to prohibitive costs.2 A major reason for increased accessibility has been the advent of biosimilar drugs, which are copies of the innovator biologic drug, however, are amenable to manufacture locally as well as not covered by any existing patents. Therefore, biosimilars are cheaper and more accessible. The recent past has seen a flooding of the local market for such biosimilar drugs. In this chapter, we discuss the impact of biosimilar agents (benefits as well as costs) and their comparability in terms of effectiveness and adverse effects, as well as issues such as nocebo effect, which potentially limit their use in patients.4 We also discuss certain peculiar adverse effects occasionally described with biosimilars.

Biosimilars and Biomimics/Biocopies
Biologic drug synthesis is complex, in that it relies on recombinant deoxyribonucleic acid (DNA) technology for synthesis of these molecules. Biosimilars are similarly synthesized using recombinant DNA technology,5 so also are biomimics or biocopies with similar molecular structure (primary, secondary, and tertiary). However, biosimilars differ from biomimics or biocopies in that they also have been demonstrated to have equivalent effect on disease states in preclinical and clinical trials, as well as demonstrate similar pharmacokinetic and pharmacodynamic properties (including immunogenicity) to the innovator biologic drugs.6
Regulatory Processes for Approval of Biosimilar Drugs

The two major agencies regulating drug approval in the world, the European Medicines Agency (EMA) and the United States Food and Drug Administration (US FDA) have laid down guidelines for the approval of biosimilar drugs. Broadly, the similar protein structure of the innovator biologic drug and the biosimilar should be demonstrable, followed by studies that demonstrate equivalence in pharmacokinetic and pharmacodynamic properties with innovators. Thereafter, efficacy and safety of biosimilar drugs with innovator biologic drugs should be demonstrated before consideration for approval. Ideally, equivalence with innovator (i.e. neither a clinically significant detriment nor benefit when compared with innovator biologic) should be demonstrated rather than non-inferiority (i.e. simply the lack of a clinically significant detriment). Furthermore, since these are foreign proteins, the lack of significant difference in immunogenicity when compared with innovator biologic drugs should also be demonstrable. Mere identity in protein structure without demonstrating the other steps mentioned simply results in a biomimic. Such biomimics have been noted to have a greater propensity to develop adverse effects than innovators, and are often in vogue in regions of the world with poor regulatory policies.7-9

The approval processes for biosimilars in India are broadly in line with the EMA and US FDA standards. This requires approvals from the Central Drugs Standards Control Organization (CDSCO).

Are Biosimilars the Same as Generic Drugs?

A common source of confusion is generic drugs and biosimilars. It is important to understand that generic drugs are mere chemicals with identical structure to the original molecules. The generation of biologic drugs has the added complexity that they require biologic systems for the generation of their recombinant protein structure; hence, they are thematically more complex to generate and attain equivalence to innovators when compared with chemical generic drugs.7

The Need for Post-marketing Surveillance for Long-term Safety of Biosimilars

An often-quoted tale of caution regarding biosimilar use has been the example of recombinant erythropoietin biosimilar, which was introduced in South America as a cheaper alternative to innovator erythropoietin analogue. This drug was primarily intended for use in patients with chronic kidney disease with anemia (which often results due to erythropoietin deficiency). Unusually, some patients treated with erythropoietin biosimilar developed pure red cell aplasia, resulting in refractory transfusion-dependent anemia.10 This was a consequence of antibodies that neutralized the effect of erythropoietin due to differences in immunogenicity of the biosimilar molecule.10 Such issues were later rectified in future erythropoietin biosimilars by modifying the protein structure to ameliorate such abnormal immunogenicity.7 This is a case in point, which reiterates the need to seek long-term safety of biosimilars that are eventually approved and marketed by means of continual post-marketing surveillance.11

Extrapolation

Another term often used in the context of biosimilars is extrapolation. Many a times, the same biologic drug is used for a number of disease states. For example, anti-TNF agents are used in RA, AS, psoriatic arthritis (PsA), inflammatory bowel diseases (IBD), and sarcoidosis. Should a biosimilar be shown to be equivalently efficacious to the innovator in RA, this is often extrapolated to assume its effectiveness to a similar degree in the other disease states it is indicated for, such as AS, PsA, and IBD. This is a common practice with biosimilars; however, due caution and careful post-marketing surveillance should accompany any such extrapolation of indication for the use of biosimilars.12

Switch, Substitution, and Re-switch

Switch refers to the decision of the treating clinician to change a biologic drug from innovator to biosimilar, or vice versa. If such a decision is taken by somebody who is not the treating physician, say, a regulatory authority or the hospital administration (due to costs or other concerns), this is instead referred to as a substitution (also known as a non-medical switch). After an initial switch, it is possible to re-switch back and forth between the two products, depending on feasibility issues such as availability, ability to afford, etc.1

Switching offers an opportunity to provide head-to-head comparisons between innovators and biosimilars. Analysis of more than 300 patients with IBD from Sweden...
switched from innovator infliximab to biosimilar infliximab CT-P13 revealed similar disease activity state at 12 months of observation. In another study from the Netherlands, 625 patients switched to biosimilar etanercept were compared with a historical cohort of 600 patients treated with innovator etanercept at the same region. Indications for etanercept use in these patients were inflammatory arthritides (RA, AS, and PsA). At 6 months, retention rates of the biosimilar (in the switched cohort) or innovator (in the historical cohort) were nearly 90%, although patients switched to etanercept biosimilar had a slightly higher risk of discontinuation. A Scandinavian biologic registry spanning five countries compared retention rates for infliximab (innovator 320, biosimilar 999 patients) and etanercept (innovator 493, biosimilar 522) in patients with spondyloarthritis. At 1-year follow-up, 66% treated with etanercept biosimilar continued the same compared with 73% treated with etanercept innovator; corresponding figures for infliximab (2-years) were 44% for biosimilar and 46% for innovator, suggesting similar rates of retention irrespective of biosimilar or innovator molecule. A comparison of more than 1,600 etanercept biosimilar switchers with more than 400 non-switchers (continuing on innovator etanercept) from Denmark for RA, AS, and PsA revealed numerically higher retention rates at 1 year for switchers than non-switchers (although of little difference in magnitude and not significant statistically). A long-term follow-up of patients for 52 weeks switched to biosimilar infliximab compared with innovator infliximab in a randomized trial (NOR-SWITCH trial) for a variety of multisystem inflammatory diseases revealed similar rates of efficacy and safety. An expected benefit of switching is lesser health-care costs; however, a recent analysis of 1620 recipients of etanercept biosimilar from Denmark did not reveal a significant cost-saving in the year following the switch compared to the year preceding it. Hence, the cost-effectiveness of switching biosimilars needs further evaluation.

**Nocebo Effect**

A perceived lesser degree of response to a drug owing to psychological or contextual factors might be described as a nocebo effect. This is thematically the antithesis of a placebo effect (i.e. perceived positive effect of a placebo, when no active drug is being administered). Biosimilar drug use in real life might be affected by the nocebo effect. In the setting of rheumatic diseases, biosimilar drugs have not shown significant differences compared to innovator drugs in blinded randomized controlled trials. However, open-label clinical trials and real-life registry data have often demonstrated lower retention rates (and higher rates of switch back to innovator drug) with biosimilars. This might be due to the perceived ineffectiveness of these drugs by the patients, which is supported by the fact that many such switches are based on subjective (rather than objective) measures of ineffectiveness. Such a nocebo effect has the potential to limit the cost-saving effect of biosimilars at an aggregated level by limiting their utilization. However, the authors perceive that nocebo effect might be a particular problem in societies where health care is nationalized. In countries like India, where a majority of the time patients pay out-of-pocket to afford biologic drugs, the lower cost of biosimilar agents is likely to reduce the likelihood of nocebo effect (since affordability now becomes the major concern rather than perceived effectiveness).

**Perspectives from India Regarding Biosimilars**

Overall published literature regarding the effectiveness of biosimilars from India is scarce. A significant chunk of the available literature relates to a biosimilar of adalimumab (ZRC-3197). Regulatory approval was obtained after proving efficacy of this adalimumab biosimilar in patients with RA when compared with innovator adalimumab. Thereafter, real life data regarding ZRC 3197 use in 51 patients with spondyloarthritis and 39 patients with RA was published. At an observation period of 1 year after treatment, more than 90% patients with spondyloarthritis had attained clinical remission. Nearly 60% of the cohort with RA also attained control of disease activity. Post-marketing surveillance under the Adalimumab Biosimilar Patient Registry (ASPIRE) further recently reported data in relation to RA and spondyloarthritis. In 73 patients with RA, significant reductions in disease activity were noted by 24 weeks; nearly one-half patients attained good control of disease activity. For 100 patients with AS treated with adalimumab biosimilar in this same ASPIRE registry, adequate control of disease activity with attainment of Bath Ankylosing Spondylitis Disease Activity Score (BASDAI) below 4 at 24 weeks of observation was possible.
BOX 1 Recommendations of the EULAR, GRS, and PANLAR regarding the use of biosimilars in rheumatology practice²²-²⁴

- Biosimilars should have lesser cost than the reference/innovator product
- Biosimilars should undergo strict regulatory processes to demonstrate equivalence in safety, efficacy, and immunogenicity with innovator molecules
- In the absence of having undergone strict regulatory processes, such drugs shall only remain as biomimics and should not be referred to as biosimilars
- Biosimilars should be preferably prescribed by their brand name to differentiate them from innovator biologics (also prescribed preferably by their brand name)
- Biosimilars should not be substituted for innovator products, or vice versa, without the knowledge of the prescribing physicians
- All patients receiving biologic drugs, whether innovator or biosimilar, should preferably be enrolled in registries
- Ongoing surveillance should be done to assess any unexpected adverse effects of biosimilars, which might be evident only after marketing

EULAR, European League against Rheumatism; GRS, Greek Rheumatology Society; PANLAR, Pan American League of Associations for Rheumatology

in more than 90% patients.²¹ Neither of these two studies identified any adverse safety signals with adalimumab biosimilar during post-marketing surveillance.²⁰,²¹ There remains an unmet need to generate and publish such real-world data in a larger number of patients for biosimilar drugs used for different indications in India.²²

Recommendations for Biosimilar Use in Rheumatic Diseases

Considering the proliferation of available biosimilar drugs worldwide for the management of rheumatic diseases, as of now various international societies have provided guidelines for the prescription of biosimilar drugs. Box 1 summarizes the relevant information from the guidelines for biosimilar use provided by the European League against Rheumatism, the Greek Rheumatology Society, and the Pan American League of Associations for Rheumatology.²³-²⁵ Briefly, these recommendations suggest that biosimilars should be cheaper than reference biologics, share similar safety and efficacy profile, undergo suitable regulatory approvals before marketing, and be subject to post-marketing surveillance.

Fig. 1: Issues related to biosimilars and their approval processes
Conclusion and Future Perspectives

Figure 1 summarizes the various issues associated with biosimilar approval and use. Despite potential advantages of biosimilar drugs in terms of cost savings and greater accessibility with similar efficacy/effectiveness and safety to innovator biologic drugs (provided they have passed through rigorous regulatory processes), the uptake of biosimilars has not been uniform. An analysis of a database from the United States of America reviewed prescriptions of innovator and biosimilar infliximab amongst patients visiting rheumatology practices. Only 3.5% patients took up infliximab biosimilar, despite this retention rates were similar to innovator infliximab. As discussed earlier, one of the barriers toward uptake or retention of biosimilars could be a nocebo effect. It is important to evaluate such factors and attempt to reduce factors, which limit their uptake despite adequate efficacy and safety. This could be facilitated by conducting qualitative research in this area. Furthermore, despite some studies showing no definitive cost-saving with biosimilars, it is reasonable to hypothesize that in a country, like India, where a majority of health-care settings use of biosimilars is out-of-pocket expenditure, it could be facilitated by conducting qualitative research in this area.

To conclude, biosimilars are a boon for India, particularly because they are cheaper and equally efficacious and safe alternatives (after appropriate regulatory approvals) and can potentially improve the sustainability of biologic use when used appropriately. At the same time, it is necessary to caution about biomimics until they have undergone appropriate regulatory approvals to prove their equivalence in safety and efficacy.

References

Abstract

Vasculitis is an immunological disorder leading to inflammation of the vessel wall. The clinical symptoms range from a mild self-limiting illness to severe life-threatening complication. Vasculitis affects blood vessels of all types and all organs. It may happen as a de novo phenomenon or secondary to other causes like infection, drugs, malignancy, and so on. Vasculitis affects all organs in the body including skin, eye, ear, nose, throat, lungs, heart, joints, etc. The clinical manifestations mimic that of a viral illness. There will be an elevation of acute phase reactants. Biopsy of the involved organ can give a clue to the diagnosis of vasculitis. Treatment includes supportive care, followed by steroids and immunosuppressants. A comprehensive approach is needed for an accurate diagnosis of vasculitis.

Introduction

Vasculitis is a group of disorder characterized by the inflammation of the vessel wall. The clinical manifestations of vasculitis range from a mild self-limiting cutaneous involvement to severe life-threatening multiorgan involvement. The diagnosis of vasculitis is difficult as the clinical presentations mimic many other illnesses and the diagnosis of vasculitis often gets delayed. A high degree of suspicion, detailed history and systematic physical examination may help in arriving at the diagnosis of vasculitis.

Epidemiology

The incidence of vasculitis in western population is 20 per million per year. The exact incidence and prevalence in India is not available. Among the various types of vasculitis, the most common is Takayasu’s arteritis and the most uncommon is Temporal arteritis. Wegener’s granulomatosis is more common in north India than south India.

Classification

Vasculitis affects blood vessels of all the types and all the organs. Vasculitis should be suspected in any patient with unexplained ischemia in the absence of atherosclerosis. Because of the increased vasculature skin is more prone for vasculitis. The vasculitis is primarily classified into two types:
- **Primary vasculitis**: It is presumed to be immune origin.
- **Secondary vasculitis**: It is mainly secondary to other causes like infection, drugs, malignancy, or idiopathic.

Chapel Hill Classification (1993)

This classification is currently considered as “Gold Standard.” See Table 1.

LIE Classification (1994)

**Primary Vasculitis**
- Vasculitis of Large, Medium, and Small Vessels:
  - Giant cell arteritis
Vasculitis of Medium and Small Vessels:
- Polyarteritis nodosa
- Churg strauss syndrome
- Wegener’s granulomatosis

Vasculitis of Small Vessels:
- Microscopic polyangiitis
- Churg strauss syndrome
- Henoch schonlein purpura
- Essential mixed cryoglobulinemia
- Cutaneous leukocytoclastic vasculitis

Miscellaneous:
- Burger’s disease
- Behcet’s disease
- Cogan’s syndrome
- Good pasteure’s syndrome
- Kawasaki’s syndrome

Secondary Vasculitis
- Infection
- Connective tissue disease
- Drug hypersensitivity
- Essential mixed cryoglobulinemia
- Malignancy
- Hypocomplementemia
- Post organ transplant

Savage Classification (1997)
See Table 2.

Causes of Vasculitis
- Immune (idiopathic)
- Infection (Bacteria, Fungus, Viral, Rickettsia)
- Drugs

Approach to Vasculitis
Vasculitis has multiple presentations. There are no definite guidelines or approach to the diagnosis of vasculitis. To diagnose vasculitis systematic approach is essential with proper history taking, clinical examination, and laboratory parameters.

- Clinical Findings
- Laboratory Findings
- Radiology
- Histology

Clinical Manifestations
Vasculitis may present with isolated cutaneous involvement or with a diffuse systemic involvement. Systemic vasculitis presents usually around 2nd to 5th decade except that Henoch schonlein purpura and Kawasaki disease in pediatric age group. Takayasu arteritis is common in young females.

General Manifestations
The clinical manifestations of vasculitis mimic like that of a normal viral illness. It includes fever, weight loss, malaise, fatigue, night sweats, generalized ache and a feel of physical unwell. These manifestations are due to the systemic inflammatory response which is produced by the release of chemical mediators from the inflamed blood vessels. These findings may not occur in patients with localized form of vasculitis.
CHAPTER 211
An Approach to Vasculitis

Systemic Manifestations

See Table 3.

Symptoms of Individual Vasculitis

See Flowchart 1.

Red Flag Signs in Vasculitis

- Polymyalgiarheumatica—classical of Temporal arteritis
- Jaw claudication during mastication—Temporal arteritis
- Stridor—Wegener’s granulomatosis
- Abdominal pain, vomiting, intestinal obstruction, bleeding
- Proteinuria, microscopic hematuria, active urinary sediment in the absence of infection
- Mononeuritis multiplex, Polyneuritis cranialis
- Acutely progressing skin lesion

Drug-induced Vasculitis

Drug-induced vasculitis should never be missed as the withdrawal of the offending drug is the main treatment. The same picture like that of isolated cutaneous involvement to diffuse organ involvement can happen with certain drugs. Some common drugs causing vasculitis are propylthiouracil, antiepileptics like phenytoin, carbamazepine, valproate, antibiotics including macrolides, quinolones, aminoglycosides, penicillins, antitubercular drugs like rifampicin and isoniazid. Several antihypertensives like hydralazine, methyldopa, nifedipine, atenolol, frusemide, diltiazem can cause vasculitis. Other drugs include heparin, warfarin, streptokinase, allopurinol, methotrexate, antidepressants. Drugs which cause ANCA positive vasculitis include hydralazine, propylthiouracil, ciprofloxacin, minocycline, phentoin, clozapine, allopurinol, sulfasalazine, D-penicillamine.

Vasculitis Mimes

- Infections—infec tive endocarditis, tuberculosis, syphilis, invasive fungal infections, viral/rickettsial infections.
- Drug induced vasculitis
- Cholesterol embolus disease, antiphospholipid syndrome, sarcoidosis, amyloidosis
- Malignancy, atrial myxoma

<table>
<thead>
<tr>
<th>Organs involved</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Pupura, Nodules, Plaques, Infarcts, Ulcers, Pyoderma gangrenosum, Widespread skin necrosis, Gangrene, Urticarial wheels</td>
</tr>
<tr>
<td>Muscles &amp; joints</td>
<td>Arthralgia, Arthritis, Myalgia, Weakness</td>
</tr>
<tr>
<td>Eyes</td>
<td>Scleritis (prelimbic area), Ring ulceration, Scleromalacia, Globe perforation, Uveitis and Retinal vasculitis, Loss of vision</td>
</tr>
<tr>
<td>Ear</td>
<td>Recurrent otitis media unresponsive to grommet insertion, Hearing loss, Recurrent ear drum perforation</td>
</tr>
<tr>
<td>Nose</td>
<td>Recalcitrant sinusitis, Nasal septal perforation, Collapsed bridge of the nose</td>
</tr>
<tr>
<td>Throat</td>
<td>Recurrent oral ulcers</td>
</tr>
<tr>
<td>Airways</td>
<td>Tracheal and bronchial stenosis</td>
</tr>
<tr>
<td>Lungs</td>
<td>Infiltrates, Nodules, Cavities, Mass lesions, Abscess, Areas of hemorrhage</td>
</tr>
<tr>
<td>Heart</td>
<td>Coronary arteritis—Kawasaki Pericardial and myocardial involvement at necropsy</td>
</tr>
<tr>
<td>GI tract</td>
<td>Mild abdominal angina, Perforation, Peritonitis, Hemobilia, Hepatic/splenic infarction, Pancreatitis</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Renovascular hypertension, Hematoma around the kidney, Glomerulonephritis, Renal failure, Proteinuria, Microscopic hematuria</td>
</tr>
<tr>
<td>Reproductive system</td>
<td>Testicular infarction, Penile ulcers on glans &amp; shaft, Scrotal ulcers</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Mononeuritis multiplex, Polyneuritis cranialis, Diffuse brain dysfunction</td>
</tr>
</tbody>
</table>
Flowchart 1: Vasculitis

Vasculitis

Small vessel vasculitis
- Purpura/ecchymosis
- Vesicles/bulla
- Livedo reticularis
- Absent pulses
- Hematuria/hemoptysis
- Mononeuritis multiplex
- Splinter hemorrhage
- Uveitis/scleritis
- Microaneurysms

Medium vessel vasculitis
- Nodules/ulcer
- Digits gangrene
- Asymmetric BP

Large vessel vasculitis
- Limb claudication
- Arterial bruit
- Aortic dilatation

Henoch-Schönlein Purpura
- Arthralgia/arthritis
- Abdominal pain
- Bloody diarrhea
- Palpable purpura

Kawasaki Disease
- Fever/conjunctivitis
- Cervical adenopathy
- Rash/mucositis
- Coronary artery aneurysm

Urticarial Vasculitis
- Arthralgia/urticaria
- Livedo reticularis
- Pruritus

Polyarteritis Nodosa
Nodules/neuropathy

Microscopic Polyangiitis
- ANCA+
- Renal/lung involvement

Granulomatous Polyangiitis
- Sinusitis/oral ulcers/recurrent otitis
- Hemoptysis
- Tracheal/bronchial stenosis
- Renal

Cutaneous Polyarteritis Nodosa
- Fever/myalgia/arthritis
- Subcutaneous nodules

Eosinophilic Polyangiitis
- Asthma/asthma
- Eosinophilia
- Neuropathy
- Pulmonary infiltrates
Investigations

Hematology

The laboratory picture of vasculitis mimic like that of an infection. ESR will be elevated. Hematology shows normocytic normochromic anemia, leukocytosis, and thrombocytosis. Eosinophilia is most common in Churg strauss syndrome. CRP will be increased.

Biochemistry

Renal function and liver function tests are helpful in determining the extent of the disease, organ damage, and therapeutic intervention. Elevated serum creatinine and decreased creatinine clearance occurs in PAN, GPA, MPA. There will be hypoalbuminemia with hyperglobulinemia. Gammaglobulinemia is predominantly of IgG type but in WG, HSP it is of IgA type. IgE levels are increased in CSS.

Urine Analysis

Urine investigations should be a must to rule out infection. Urine may show proteinuria, hematuria, and cylindruria. ANCA associated vasculitis may show active urinary sediment with red cell casts.

As the treatment of vasculitis involves the use of immunosuppressants, infections should be ruled out as it can lead to disastrous complications. Procalcitonin is a good diagnostic tool to rule out vasculitic mimic like infection. It will be elevated in infections rather than non-infective inflammatory etiology. But the cost and availability hinders its usage. Apart from the basic workup, specific autoimmune workup has to be done for further evaluation.

Serology

Rheumatoid factor is frequently positive in vasculitis. Very high titre of rheumatoid factor is a hallmark of systemic rheumatoid vasculitis. ANA will be positive in high titres in SLE, Systemic sclerosis, Sjogrens syndrome, and Overlap syndrome. hepatitis B, hepatitis C is a must to rule out classical PAN, cryoglobulinemia vasculitis. Anti GBM antibody will be positive in Good Pasteur’s syndrome.

Antineutrophil Cytoplasmic Antibodies (ANCA)

ANCA is specific diagnostic tool for diagnosing vasculitis. ANCA is done by indirect immunofluorescence/ELISA.

TABLE 4

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Antibodies directed against</th>
<th>ANCA and its specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>C–ANCA</td>
<td>Anti-serine protease 3(PR3)</td>
<td>Wegner’s (&gt;90%) MPA (100%) CSS (50–60%)</td>
</tr>
<tr>
<td>P–ANCA</td>
<td>Anti-myeloperoxidase (MPO)</td>
<td>MPA (70–90%)WG(&lt;10%)</td>
</tr>
<tr>
<td>Atypical ANCA</td>
<td>Lactoferrin, cathepsin G, elastase, lysozyme</td>
<td></td>
</tr>
</tbody>
</table>

During the acute phase of vasculitis, ANCA will be positive in very high titres. But, ANCA has a poor correlation between titres and clinical disease activity. There are three different patterns of ANCA shown in Table 4.

Imaging

X-ray Chest

Nodular, cavitating infiltrates is characteristic of Wegner’s granulomatosis. Vasculitis must be included in the differential diagnosis, when there is unresolving, rapidly progressive consolidation during adequate antibiotic/ATT. Rapidly enlarging parenchymal lesion suggestive of pulmonary hemorrhage is characteristic of Wegner’s granulomatosis, microscopic polyangiitis.

CT/MRI/PET Scan

The above imaging modalities are used in the diagnosis, delineation of disease extent, identification of biopsy site, and monitoring response to therapy.

FDG PET scan will help in detection of aortic wall inflammation.

Angiography

Angiography defines the extent of disease involvement. It is also useful in classifying the type of vasculitis, identifying the areas for intervention like angioplasty and stent insertion. It is important in large and medium vessel vasculitis. It shows the pathognomonic visceral aneurysms in Polyarteritis nodosa.

2D Echo

Done to rule out left ventricular dysfunction, myxoma.
Histology

Skin Biopsy
Skin biopsy may show features suggestive of inflammation. The same histology may be seen in patients with benign cutaneous vasculitis and SNV. For ideal histopathological examination, sample should be taken less than 48 hours of onset of symptoms. Nodular skin lesions and involved muscles are preferred sites for PAN.

Renal Biopsy
Granulomatous inflammation in tissue biopsy is suggestive of Wegner’s granulomatosis.

Nerve Biopsy
Vasculitis of the vasa vasorum is characteristic of mononeuritis multiplex. Sural nerve biopsy is indicated if peroneal neuropathy is seen on electromyography. In giant cell arteritis, Temporal artery biopsy is done. Biopsy of subclavian artery is done in Temporal arteritis.

Mucosa of Sinus and Nose
As vasculitis is a patchy process, it may be easily missed in a small biopsy.

Open Lung Biopsy
It is a highly rewarding procedure. Pulmonary tissue biopsy is highly specific for Wegener’s granulomatosis.

Treatment

General Measures
Avoid stress, bed rest, and keep extremities warm. Avoid smoking in case of severe pulmonary involvement. Antihistaminics to reduce itching and NSAIDs to decrease pain.

Specific Therapy
- **Antibiotics**: To control infections according to culture and clinical profile.
- **Drug**: Stop the offending drug in case of drug induced vasculitis.
- **Dapsone**: It can be used as the initial agent for CSVV in the absence of systemic involvement (Dose: 50–200 mg/day in divided doses). The response can be observed within 2 weeks. In urticarial vasculitis dapsone can be combined with indomethacin or hydroxychloroquine.
- **Hydroxychloroquine** (200–400 mg/day): It can be used in HUV but not in other small vessel vasculitis.
- **Corticosteroids**: Low dose steroids (<10 mg on alternate days) are used to reduce the inflammation in patients not responding to steroids in small vessel vasculitis. High dose systemic steroids are indicated in severe necrotic/ulcerative cutaneous lesion, acute glomerulonephritis, peripheral neuropathy with impending palsy and gastrointestinal bleeding.

Steroid has a good response in HSP in preventing nephritis as well as improves the outcome of existing nephritis. In classic PAN disease control can be achieved with steroids. In HCV associated cutaneous vasculitis, short-term systemic steroids are beneficial in controlling renal and CNS manifestations. Steroids should be short term in virus associated vasculitis in order to prevent the risk of viral replication.

Steroids show a good remission. It helps in decreasing the infection rate, cumulative dose of cyclophosphamide to achieve remission and decrease rate of secondary malignancy. Temporal arteritis shows a very good response to steroids. After remission it can be maintained with immunosuppressants like azathioprine or methotrexate. Systemic steroids are contraindicated in Kawasaki disease to avoid coronary aneurysm formation.

 Intravenous pulse steroid (methylprednisolone 1 gm/day for 3 days) therapy is indicated in life threatening organ involvement in diseases like WG, MPA, CSS.
- **Cyclophosphamide**: Between 2–3 mg/kg/day. It can be continued for a year after remission was attained. The side effects are hemorrhagic cystitis, bladder cancer, marrow toxicity. There is an increased occurrence of relapse after withdrawal of the drug.
- **Alternative regimen is intermittent “pulse” Cyclophosphamide therapy (750 mg/m²) every 2–3 weeks initially for 2–3 doses every 4 weeks till 6 pulses.**
- **Azathioprine**: It prevents recurrence in CSSV either used alone or in combination with steroids.
- **Rituximab**: Used in frontline drug in patients with HSP. Two doses 1 gm each with an interval of 2 weeks. It gives prolonged remission.
Antivirals: Interferon α is the preferred drug in hepatitis C virus associated CV. Significant improvement has been documented with decrease in cryoglobulin levels. Ribavirin may be used for treatment as well as in prevention of relapse in hepatitis C induced vasculitis.

Immunoglobulins: It may be of use in Kawasaki disease. Dose: 2 g/kg single dose in combination with aspirin. Early administration prevents the risk of aneurysm formation. c-PAN was treated successfully with IVIg (2 g/kg over 2–5 days), but relapse rate is common.

Plasmapheresis: It is helpful in cryoglobulinemia and hepatitis B related classical polyarteritis nodosa in severe cases refractory to other treatments.

Mycophenolate Mofetil: Used in steroid dependent, steroid resistant cases of HSP, especially with renal complications.

Deoxyspergualin: Monoclonal antibodies have a variable success rate.

Infliximab: Used in steroid non-responsive necrotizing CSSV.

Conclusion

The mortality and morbidity related to vasculitis is mainly due to late diagnosis. As the symptoms are very subtle at the initial stage, there is a delay in the suspicion and diagnosis of vasculitis. Treatment is individualized. A comprehensive approach is needed for successful management of vasculitis.

References

Abstract

Rheumatoid arthritis is the most common disease affecting the musculoskeletal system and the immune-inflammatory cascade causes avalanche of detrimental effects to the human systems. Incidence appears to be increasing worldwide and treat to target after early identification of the condition remains the current approach to tackle RA. DMARDs have been the conventional drugs of choice for years together and with the advent of cytokine inhibitors since 2000, prognosis and outlook of immune mediated diseases have improved remarkably. Biologics and Biosimilars have revolutionized the management of RA; however, DMARDs remain the gold standard care for these patients. This article focuses on the management of patients with RA who fail to respond to DMARDs.

Introduction

Rheumatoid arthritis (RA) is the most common of all arthridies and current incidence in India is increasing. The prevalence of RA was available from only four studies, ranging from 0.28% to 0.7%.1 Literature review suggests the RA prevalence, based on the ACR criteria, ranged from 2.8 per 1,000 to 7 per 1,000, varying throughout India. Patients with RA taking disease-modifying antirheumatic drugs (DMARDs) ranged from 11% to 100%, with the majority of the studies reporting proportions more than 75%.1

Various studies report that the DMARDs available to the patients in India include the methotrexate (1990), leflunomide (2001), and sulfasalazine (1998).2,3 Shankar et al. reported that on comparing the characteristics among erosive and non-erosive RA patients in northern India, the median DMARD-naive time period was recorded as 3 years among patients with erosive disease and 2 years among those without erosive disease.4 Shankar and colleagues reported again in a study focused on only female RA patients, the median DMARD-naive time period was 3 years.5

RA occurs frequently in females and around 30 new patients per Lac population each year are diagnosed with RA. Stress and environmental triggers may trigger the disease onset. About 5% of first degree relatives are at risk of developing RA.6 Cigarette smoking, coffee, and oral contraceptive pills appear to increase the risk of development of RA.7 In developing countries due to various factors in accessing medical help, delayed diagnosis occurs thereby causes functional disability and reduced quality of life.8

Diagnosis and Current Management

Rheumatoid arthritis, most common form of inflammatory arthritis is usually diagnosed by the presence of joint swelling, raised inflammatory markers, positive anti CCP and imaging evidence of erosions, if required. Ultrasonogram and MRI have been beneficial in identifying the early changes in the synovium and marrow.9

Currently RA is managed using multimodality treatment. Diet, counseling, physiotherapy, and occupational therapy compliment drug treatment.
Drug management aims to relieve symptoms as soon as possible followed by disease modification that slows or stops radiological progression, which is closely correlated with progressive functional impairment.

*Disease modifying conventional drugs* included methotrexate (10–15 mg) given weekly once, sulfasalazine (1–2 gm), leflunomide (10–20 mg) and iguratimod (25–50 mg). Monitoring of bloods for patients while on DMARDs will have to be done every 4 weeks for 2 months and then once in 3 months.

**Poor prognostic factors:**

- Persistently moderate or high disease activity despite DMARDs
- High ESR < CRP
- Presence of high titers of RF and/or ACPA
- Presence of early erosions

Evidence points to reduced compliance to oral DMARDs and also effective in two-thirds of patients with RA while achieving remission. Hence, there is unmet need to improve the patients health, quality of life, and induce remission for the remainder of population with RA.

**Causes for DMARDs Failure in RA**

- Compliance issues
- Cost factors
- DMARD intolerance issues
- Comorbidities
- Fear of toxicities and long-term side effects

As RA is chronic and long-term drug treatment is necessary, it is important for the physicians to explore the patients understanding and family support in daily life. Compliance can be a problem due to fear of side effects driven by the society or cost issues or intolerance to DMARDs. Few patients may have comorbidities that might preclude to effective DMARD therapy. Hence, it is imperative to explore all these factors before we call as DMARD failure.

Clinical disease activity should be measured using DAS 28 ESR score—including swollen joint, tender joint, VAS scale, and ESR.

**How to Manage the Resistant RA?**

International guidelines including American College of Rheumatology (ACR), British Society of Rheumatology and NICE guidance (BSR), European League of Association of Rheumatologists (EULAR) have supported the use of various biologics in patients with resistant rheumatoid arthritis and evidence has shown time and again that Biologics have achieved remission and improved the quality of life.

Before starting on biologics, we must ensure adequate optimization of oral DMARDs with regards to dose, compliance, and side effects. Many occasions, patients do not share the compliance issues, and hence it is important to explore the problems in taking DMARDs and address those issues.

Biologics are expensive to most patients in India as developing nation; therefore, biosimilars tend to be preferred in patients who can afford. Evidence shows approved biosimilars are equally efficacious in the management of various inflammatory rheumatic diseases.

**Biologics and Biosimilars**

We have seen tremendous developments in the use of biologics and biosimilars during the last decade and monoclonal antibodies are used in various rheumatic diseases with Treat to Target approach.

Biologic therapies have been used in various inflammatory rheumatic diseases like RA, spondyloarthritis (SpA), psoriatic arthritis, ANCA associated vasculitis, and osteoporosis.

Biosimilars are similar to biologics intended to offer comparable safety and efficacy to the reference molecule. They are often manufactured in cell lines and subject to modification like glycosylation. Biosimilars must be shown to be identical to innovator biologics based on data from clinical and analytical studies.

Methotrexate remains the anchor drug for RA, which has been proven to reduce anti-drug antibodies and also retains radiological remission.

The list of currently licensed biologics for use in RA is shown in Table 1.

**Pretreatment Screening**

Although biologics and biosimilars can be used in various indications in rheumatology, patients need to be screened for TB, Hepatitis, and HIV. They also need to be vaccinated against hepatitis, chickenpox, influenza, and pneumonia.

Screening tests include blood count, CRP, LFT, renal function tests, hepatitis B, C screening, mantoux, and immunoglobulins for rituximab. ECG and ECHO when appropriate.
Contraindications for use of biologics:
- Uncontrolled heart failure, multiple sclerosis, active infections, Hep B, and Hep C positive and untreated cancers.
- Previous septic arthritis, pregnancy, and lactation.
- Risk of TB has been found to be more in Asian countries. 21

Nearly a decade of experience in using biologics and biosimilars has given a wide range of choices for patients with RA and those drugs are used in India and gaining acceptance too. 22

**What do we do if not Affordable to Biologics or Biosimilars?**
Recently RA affects women and men of both socioeconomic groups and being a chronic disease it’s understandable for patients with low income to default on DMARDs. Hence, it would be prudent to consider low dose long-term steroids and NSAIDs along with monotherapy like methotrexate for disease remission, 23 after having explained the risk for diabetes and stomach upset.

**Conclusion**
DMARDs are effective in RA, but resistant rheumatoid needs careful approach to devise the management program tailor made to the patient and holistic intervention is required that includes biologics/biosimilars, physiotherapy, and yoga. Apart from disease remission and improved quality of life, we also need to achieve cardiovascular risk reduction and healthy family life.

### References

IgG4-related disease is a chronic inflammatory condition characterized by tissue infiltration with IgG4-secreting plasma cells. It manifests as organomegaly, fibrosis, and organ dysfunction. Elevated IgG4 level in blood gives an important clue to the diagnosis. CD4+ cytotoxic T cells and plasmablasts are central to the pathogenesis, and IgG4 antibody may be a bystander. Biopsy is essential for diagnosis whereas CT, MRI, and PET scan help in defining the extent of the disease. Response to steroid is excellent. Steroid resistant cases are treated with Rituximab.

Introduction
Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is a multiorgan immune mediated fibroinflammatory condition of unknown etiology. It was in 2013 in an international symposium that term IgG4-RD was adopted.1

Epidemiology
Due to the low awareness of disease, there is difficulty in ascertaining the epidemiology of the disease. IgG4-RD has an elderly and male preponderance (Male:Female 3:2).2 It tends to involve pediatric age group less commonly. Presently, there are not much epidemiological studies on IgG4-RD in India.

Pathogenesis
The pathogenesis of IgG4-RD suggests about disease to be autoimmune in nature though incompletely understood. In the past it was suggested that IgG4-RD to be T helper cell-2 (Th-2) mediated condition. But the concept of Th-2 memory cells circulating in IgG4-RD presently has been rejected since only a small subset of patient of IgG4-RD having atopy had this feature. Recently, researchers noticed that CD4+ cytotoxic T lymphocytes, which are clonally expanded, are found in both peripheral and fibrotic lesion of IgG4-RD.3 The cytotoxic T cells release interleukin-1 (IL-1), transforming growth factor-beta (TGF-beta) and Interferon gamma and these cytokines/chemokines are responsible for increased fibrosis, which is the dominant part of IgG4-RD.

Further, the disease has a sustained CD4+ cytotoxic T cells effect due to continuous antigen presentation by B cells and plasmablast. In addition to CD4+ cytotoxic T lymphocyte effect, there is also a follicular helper T(Tfh) response that is responsible for development of germinal centers (within the lymph node/involved organ) and production of cytokines (esp IL-4). The germinal center/ cytokine drives the IgG4 class switch, producing IgG4 plasmablast and long lived plasma cells.4 The IgG4 antibodies positivity in IgG4-RD is due to the downregulating response to another primary process.

So IgG4 antibodies are not pathogenic of IgG4-RD, rather CD4+ cytotoxic T lymphocytes and plasmablasts play central role in the pathogenesis.
Clinical Features

The symptomatology in IgG4-RD is based on organ/s affected. It is subacute in onset. Clinical presentation in IgG4-RD is due to the resultant inflammatory infiltration/fibrosis, which cause the tissue or organ dysfunction. Additionally, tumor like effect may cause obstructive/compressive complications. Despite the multiorgan involvement, four clinical types can be more commonly identified. These are:

- **Group 1:** Pancreato-hepatobiliary disease
- **Group 2:** Retroperitoneal fibrosis and/or aortitis
- **Group 3:** Head and neck limited disease
- **Group 4:** Classic Mikulicz syndrome with systemic involvement

Symptoms of asthma or atopy may be present but fever is rare. Salivary and lacrimal glands, pancreas, biliary tract, and kidney are commonly involved.

Auto immune pancreatitis (AIP) is of two types. In the context of IgG4-RD, type 1 AIP is generally a pancreatic disease and biliary tract involvement (mimicking Primary Sclerosing Cholangitis) in combination.5

IgG4-RD commonly involves retroperitoneal tissue often resulting into fibrosis. This fibrosis may result in obliteration of adjoining structures (aorta and ureter).

Eye involvement (25–50%) in IgG4-RD usually presents as a mass (orbital pseudotumor) due to dacryoadenitis or MALT lymphoma.

Major salivary gland (parotid/submandibular) involvement mimics Sjögren syndrome, although in IgG4-RD the symptoms of dryness of eyes and mouth are milder along with seronegativity for anti Ro/La antibody.

Lung involvements are often asymptomatic or may present with respiratory-related symptoms. These symptoms may be due to the alveola/interstitial involvement or due to opacities (ground glass/nodular). The pulmonary manifestations of IgG4-RD may mimic sarcoidosis.

Kidney involvements related to IgG4 are tubulo-interstitial nephritis (TIN). Membranous nephropathy is much less common. IgG4-related TIN presents with profoundly hypocomplementemia (due to the complement activation by other IgG subclasses—IgG1 or IgG3).

Riedels thyroiditis is IgG4-RD of the thyroid gland disorder.

Cutaneous pseudolymphoma, hepatopathy, gastritis, sclerosing mastitis, central nervous system involvement (esp. patchy meningitis) with or without hypopituitarism, prostatitis, IgG4-related disease of the ovary, constrictive pericarditis, generalized lymphadenopathy are other organ presentation described.

Laboratory Tests

If there is a suspicion of IgG4-RD one should start work up with routine blood investigations, IgG4 level, imaging studies and finally tissue biopsy, if possible.

Blood Tests

Blood investigations usually reveal hypergamma-globulinemia. Peripheral blood shows eosinophilia with elevation of serum IgE (especially in presence of atopy) and IgG4 level. Serum IgG4 levels can also be elevated in other conditions, which may mimick IgG4-RD.6

Plasmablast concentration is a better marker than IgG4 level, as it predicts response to treatment and also relapse.7

Hypocomplementemia is particularly common in IgG4-related kidney disease as well as with mild proteinuria.

Serum amylase and lipase may be planned if pancreatitis is suspected.

Imaging

On contrast enhanced CT, lesions look homogeneous with well-defined margins.

MRI (T2-weighted) shows hypointense to isointense images depending upon fibrosis/cellularity.

Increased metabolic activity on FDG-PET/CT helps in locating the extent of involvement.

Histology

Findings include lymphoplasmacytic infiltrate, storiform fibrosis (cartwheel appearance of the arranged fibroblasts and inflammatory cells) and obliterator phlebitis.8 In addition, an increased number of IgG4-positive plasma cells greater than the cut-off point and elevated IgG4/IgG cell ratio more than 40% needs to be proven. There may be modest tissue eosinophilia.

Diagnosis

IgG4-RD is diagnosed by a combination of clinical (organomegaly), serologic (increased IgG4 level), radiologic (masses on CT, MRI), and pathologic findings (as described above). Biopsy of the involved organ is
crucial for diagnosis. Japanese comprehensive clinical diagnostic criteria (CCD) 2011 are used for diagnosis. Organ-specific diagnostic criteria is used when CCD criteria does not properly fit in for the diagnosis of IgG4RD.

**Differential Diagnosis**

The major disorders that should be distinguished from IgG4-RD are cancers (pancreatic cancer, cholangiocarcinoma), primary sclerosing cholangitis, connective tissue disease like (Sjögren syndrome, granulomatosis with polyangiitis), Castlemain disease, idiopathic RPF, and infectious aortitis.

**Treatment**

Treatment should be initiated early to impede the progress from the inflammatory to fibrotic stage (treatment nonresponsive). There is no international consensus on treatment guideline at present. The approach to treatment in IgG4-RD is discussed here.

**Pretreatment Evaluation**

Evaluation of the extent of disease after establishing the diagnosis is desired before initiating treatment, so baseline investigations are desired pretreatment. These are:

- Complete blood count, RFT, LFT, serum amylase and lipase, IgG subclass levels—esp IgG4, IgE concentration, serum C3 and C4 concentration, HbA1c.
- Fecal elastase in pancreatic involvement.
- Urinalysis to document asymptomatic proteinuria related to TIN.
- Imaging—CECT/PET scanning to determine the extent of disease.

**Initial Therapy**

All symptomatic or those with progressive disease should be started on therapy. The others—asymptomatic, non-progressive and limited disease need serial watchful waiting approach.

**Steroid**

Glucocorticoids are the drug of choice for initiation, unless contraindicated. The initial recommended oral dose of prednisolone for remission induction is 0.6 mg/kg/day for 2–4 weeks followed by tapering to 2.5–5.0 mg/day over a period of 2–3 months. Steroid pulse therapy is considered for acutely ill patients.

In the early stage of disease majority responds to glucocorticoids (decrease in size of mass, betterment of organ function, decrease in IgG4 value), though duration of response remains variable. But disease flare is seen during or after tapering of glucocorticoids. Also, patients with fibrotic changes respond poorly.

**Rituximab**

Patients with multiorgan disease (≥3 organs) or extremely high serum IgG4 concentration (>5 times UNL) are very likely to require an agent other than glucocorticoid alone for induction of remission. Rituximab (anti-CD20 antibody) is effective for both induction and maintenance in a dose: 1 g IV for a total of 2 doses 2 weeks apart.10

Rituximab do not directly kill plasma cells as they lack the CD-20 receptor. It acts by depleting the pool of CD20+ progenitors—either naïve B cells or memory B cells. Thus, it wipes out plasmablasts, which have a short lifespan. This loss of plasmablast results in decrease in IgG4 production.

**Maintenance Therapy**

High relapse rate is reported with multiorgan disease or extremely elevated IgG4 level. An IgG4-RD responder index (RI) has been developed to predict relapse. Low-dose prednisolone (2.5–5 mg/day) needs to be continued as maintenance therapy to avoid relapse for a period of at least 3 years, but keeping watch on steroid related complications. However, in case of relapse initial dose of steroid is recommended.

Mycophenolate (up to 2.5 g/day) and azathioprine (2 g/kg/day) are the other options for maintenance therapy. Rituximab is very effective as maintenance therapy especially where steroid and other immunomodulator fails. It has a very low relapse rate. The reason being memory B-cell count appeared to be unaffected by steroid treatment, therefore partly explaining why the maintenance of remission in IgG4-RD often fails during glucocorticoid withdrawal.

**Surgery**

Selectedpatientsmayrequire surgerylike—hydronephrosis due to ureteral obstruction in retroperitoneal fibrosis/obstructive jaundice due to sclerosing cholangitis requires biliary stenting and drainage/aortic aneurysm in aortitis/
compressive symptoms in Riedell’s thyroiditis/vascular and organ compression from sclerosing mesenteritis requires debulking surgery.

**Prognosis**

IgG4-RD has a variable course. Some treatment naïve patients are reported to have spontaneous remission though short lasting. Whereas, most of them have relapse/chronic progression at variable rate. Baseline levels of serum IgG4, IgE, and eosinophil serve as markers for relapse prediction. Non-treatment results in a significant morbidity and mortality due to irreversible damage of organs and its sequelae because of the associated fibrosis. There is a divided opinion regarding increased risk of malignancy with IgG4-RD.

**Conclusion**

So to conclude, IgG4-RD results in a subacute multiorgan dysfunction/enlargement. The diagnosis is made in a background of clinical features which shares specific serological and pathological findings. Measurement of plasmablast concentration correlates better than IgG4 level with disease activity and is a promising tool to be used in future. A good initial response to steroid is a characteristic behavior of the disease, steroid needs to be tapered over a period of 2 months and any relapse or failure to the initial response, Rituximab holds a good promise.

**References**

Abstract
Systemic lupus erythematosus (SLE) is a multi-system connective tissue disorder where immunosuppression is the mainstay of therapy. Steroids, although effective immunosuppressant, have a lot of side effects in the long run. Thus, there is a need of steroid sparing immunosuppressive agents for long-term therapy in SLE. In the first part of this chapter, the conventional steroid sparing drugs like Methotrexate, Cyclosporine, and Mycophenolate, which have been mentioned in the 2019 EULAR guidelines, have been discussed in details. In the second part of this chapter, newer therapies like Voclosporin, anifrolumab, Belimumab, and Baricitinib have been discussed along with the recent clinical trial results. Lastly, newer frontiers of therapy like Glucocorticoid induced leucine zipper (GLIZ) and other experimental drugs have been explained. Discussion of each drug is also associated with mention of the dose and side effects.

Introduction
Systemic lupus erythematosus (SLE) is a multisystem connective tissue disorder with considerable mortality and morbidity. Since it mainly affects the young adult, economically productive, age group, the financial burden of this disease is also significant. Treatment of this disease continues for a long time, sometimes even lifelong. With developments in immunology and medical genetics, our understanding of the pathogenesis of this disease is also evolving. This is opening up newer avenues for therapeutic target.

SLE is a disorder of autoimmunity. Thus, immunosuppression or immunomodulation in various forms is the mainstay of therapy. In the early days, the main drug used for this purpose was steroids. While steroid is an effective immunosuppressant and quite effective in saving lives (especially in acute flares), it also has a lot of side effects in the long run (Table 1).

Thus, for long-term treatment, steroids are not an ideal choice. The current SLE guidelines also advice quick tapering of oral steroids to avoid these side effects.

The mainstays of SLE therapy, especially in acute flares, are cyclophosphamide and steroids with steroid sparing drugs like Azathioprine and MMF for maintenance. But in spite of quick diagnosis and early treatment, mortality from SLE is still very high. In 2017, Jorge et al. from the Harvard Medical School published an article, which showed that over 15 years, between 1999 and 2014, the mortality from SLE has not been decreased appreciably. As early as in 2000, researchers from Baltimore, USA, had also shown that long-term steroid therapy in SLE is associated with significant organ damage. Thus, it is evident that the current therapies including steroids are not adequate and there is a large unmet need in SLE management.

Conventional Agents
There are many drugs, besides steroids, which are used in SLE. They include hydroxychloroquine (HCQ), mycophenolate mofetil (MMF), azathioprine (AZT), cyclophosphamide, methotrexate (MTX), cyclosporine (CYC), and tacrolimus (TAC). But they are all not equally effective. HCQ is used as a background therapy but it is...
CHAPTER 214
Treatment of SLE beyond Steroids

TABLE 1
The different systemic effects of long-term steroid use

<table>
<thead>
<tr>
<th>Musculoskeletal</th>
<th>Endocrine</th>
<th>Cardiovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Osteoporosis</td>
<td>• Dysglycemia</td>
<td>• Edema</td>
</tr>
<tr>
<td>• Myopathy</td>
<td>• Cushingoid features</td>
<td>• Hypertension</td>
</tr>
<tr>
<td>• Osteonecrosis</td>
<td>• Adrenal suppression</td>
<td>• Premature atherosclerosis</td>
</tr>
<tr>
<td></td>
<td>• Growth failure in children</td>
<td>• Arrhythmia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ophthalmologic</th>
<th>Psychiatric</th>
<th>Dermatologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cataract</td>
<td>• Depression</td>
<td>• Acne</td>
</tr>
<tr>
<td>• Glaucoma</td>
<td>• Hypomania</td>
<td>• Hirsutism</td>
</tr>
<tr>
<td>• Central serous chorioretinopathy</td>
<td>• Sleep disturbance</td>
<td>• Skin thinning</td>
</tr>
</tbody>
</table>

TABLE 2
2019 EULAR recommendations for non-steroid drugs in SLE

<table>
<thead>
<tr>
<th>Main target of treatment</th>
<th>HCQ</th>
<th>MTX</th>
<th>AZT</th>
<th>MMF</th>
<th>CYC</th>
<th>IV Ig</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>To be used in all patients (5 mg/kg), long term; if HCQ intolerant, quinacrine</td>
<td>To be added when symptoms not controlled with HCQ+GC; once weekly dose; 10–25 mg/week</td>
<td>To be added when symptoms not controlled with HCQ+GC; safe in pregnancy; 2–3 mg/kg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low disease activity status (if remission is not obtained)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention of flares</td>
<td></td>
<td></td>
<td></td>
<td>Can be used for both induction and maintenance; not effective in neuropsychiatric lupus; costly; discontinue 6 weeks before planned pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention of flares</td>
<td></td>
<td></td>
<td></td>
<td>Induction: 3 g/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Maintenance: 1–2 g/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYC</td>
<td>Used in moderate to severe disease activity; avoid in severe renal disease; 1–3 mg/kg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AZT, azathioprine; CYC, cyclosporine; GC, glucocorticoids; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; MTX, methotrexate.

not effective in acute flares or life threatening conditions. A French study (PLUS) in 2013 found that HCQ is unable to prevent life threatening flares.4 But this does not mean that HCQ is a non-essential drug in SLE. Continuous HCQ is effective in preventing flares of skin rashes or arthritis and this drug should be given to all lupus patients (Table 2).5 AZT and MMF are both steroid sparing agents. In the MAINTAIN trial, both of them were found to be equivalent in preventing relapse of nephritis in SLE.6 In the ALMS study, MMF was found to be equivalent to IV Cyclophosphamide in inducing remission in renal flares.7 Thus, although cyclophosphamide (in NIH or Euro-Lupus protocol) remains the mainstay of rescue therapy in renal flares, MMF may be tried as an alternative. AZT is mainly used to help reduce the dose of oral steroids. It is safe in pregnancy (in contrast to MMF that must be stopped at least 6 weeks before conception) but neutropenia may be a rare, yet serious, adverse reaction.

There have been very few studies of MTX in SLE. A 2014 systematic review concluded that MTX is effective in treating arthritis and mucocutaneous manifestations of SLE and it also helps to reduce the dose of oral steroids.8 Another study from Germany also depicted that SLE patients, who had not improved despite 6 months of oral steroids, did respond to oral MTX 15 mg/week.9 There was not much side effect of MTX in this regimen. However, the efficacy of MTX in lupus nephritis is still debatable.10
Cyclosporine, a calcineurin inhibitor (CNI), is another drug, which has been tried in SLE. Although this is a good immunosuppressant, it has common side effects like hypertension and nephrotoxicity, which makes it unsuitable for high-dose therapy. But low-dose maintenance therapy can always be used in SLE. There are very few RCTs with CYC in SLE. These have shown that CYC is effective in decreasing proteinuria and improving renal function. Also, the doses of other immunosuppressants and steroids could be reduced when CYC is used long term. Some studies have also shown that CYC may improve the renal histology in lupus patients. However, the serological markers like anti-ds-DNA or complements do not change appreciably with CYC. One reason may be that CYC mainly acts on T-cell subset with very little effect on the humoral immunity. But despite persistence of serological abnormalities, clinical improvement occurs after CYC use.

Tacrolimus, another CNI, till now used in organ transplant recipients, is now being used in combination with steroid as well as MMF in refractory proteinuria. Several small studies have looked into the use of TAC in Class III, IV, and V lupus nephritis, both as induction and as maintenance therapy in patients refractory to other treatment. Majority were Asian patients. Another study by Szeto et al. in 18 patients with biopsy proven Class V lupus nephritis treated with TAC 0.1 to 0.2 mg/kg/day with tapering doses of prednisolone showed 76.2% decrease in proteinuria compared to historical control group treated with cyclophosphamide or azathioprine. Side effect profiles are same as CYC with glucose intolerance.

IV Ig use is still considered experimental in SLE. A 2014 meta-analysis found that IV Ig is effective in reducing disease activity. In some studies, it has also been shown to be effective as a steroid sparing agent. But till now, only a few studies have assessed IV Ig for lupus nephritis. The results have been mixed. Thus, it is an uncommon choice in acute renal flares.

Table 2 gives a summary of the 2019 EULAR recommendations for the use of non-steroid drugs, as discussed earlier, in SLE.

**Newer Agents**

The drugs discussed above are effective in controlling disease activity in many cases but still a large percentage of SLE patients continue to have flares and worsening of organ failure. However, there are newer therapies in the horizon for SLE. These will be discussed next.

A newer analog of CYC, which is in development, is Voclosporin. This drug was first developed in the 1990s, but its potential uses are being investigated only recently. In January 2019, Rovin et al. published the results of the AURA-LV study, where Voclosporin was used in addition to MMF and rapidly tapering oral steroids for induction therapy in lupus nephritis. The dose of Voclosporin used was 23.7 mg (low dose) or 39.5 mg (high dose) BD. It was found that there was significantly high complete renal remission (CRR) rate in the Voclosporin group (both low and high dose) and this advantage was sustained at 48 weeks. Very recently, in March 2020, Aurinia Pharmaceuticals, the company promoting Voclosporin, announced the results of the AURORA study. This was a Phase 3 Global RCT, which assessed the efficacy of Voclosporin in addition to MMF and rapidly tapering oral steroids for induction phase. The results showed that Voclosporin was effective in inducing a superior and faster renal response. The side effect profile in the AURORA trial was similar to standard therapy. There was no excess mortality. In this trial, the dose of Voclosporin was 23.7 mg BD. Thus, if this new drug is approved, it may be a valuable addition in SLE treatment strategy.

Type I interferon (INF) is known to be an important mediator in the pathophysiology of SLE. Recently, an inhibitor of the type 1 IFN receptor, Anifrolumab, has been developed. In January 2020, Morand et al. published the results of a trial of Anifrolumab in active SLE (TULIP-2 trial). Anifrolumab (300 mg) was given i.v. every 4 week for 48 weeks. At 52 weeks, there was significantly more response (assessed by BILAG) in Anifrolumab group compared to placebo. Anifrolumab mainly helped in reduction of the glucocorticoid dose and decreasing severity of skin disease. But there was not much difference in tender joint count. This was the first successful trial of a biological drug in SLE since Belimumab almost a decade ago. The first trial with Anifrolumab was the TULIP-1 trial, published in the Lancet, in 2019. In this trial, the primary end point was SLE responder index (SRI-4) at 52 weeks. But this first trial was, however, a failure as there was no difference in SRI-4 between the groups. But secondary end-points like reduction in corticosteroid dose and BILAG response were achieved. The researchers then quickly published the results of the second trial (as
mentioned earlier) where favorable results were shown. Anifrolumab is generally safe for human use. But in 2017, a Phase IIb trial with the drug found some excess incidence of Herpes Zoster and influenza, compared to placebo. The maker of the drug, AstraZeneca, plans to move ahead with application for approval although expert opinion is still divided about potential efficacy of the drug.

Belimumab, which was approved by the FDA in March 2011, is the first targeted biological therapy for active SLE. B lymphocyte stimulator (BLyS) is a costimulator for B-cell survival and function (Fig. 1). It is expressed by a variety of cells like macrophages and is also found in soluble form in tissues. BLyS receptor is present on B-cells, the most important receptor being BR3. Interaction of BLyS with BR3 prevents apoptosis of B-cells and promotes autoantibody production. Overexpression of BLyS increases activity of autoreactive B-cells and this is important in the pathogenesis of autoimmune conditions like SLE. Belimumab is a human monoclonal antibody against BLyS. Binding of belimumab with BLyS prevents its interaction with BR3 and thus, reduces B-cell survival and antibody production. There have been two Phase III trials of Belimumab in SLE: BLISS-52 and BLISS-76. The numbers (52 and 76) indicate the number of weeks for which the study subjects were followed up. While both the studies demonstrated efficacy of the drug, it was also seen that the effects were not sustained at 76 weeks. The dose of the drug is 10 mg/kg, given i.v. at weeks 0, 2, 4, and then monthly. It is used with standard therapies like MMF. But one problem of the drug is that, in the trials, it was not studied in active lupus nephritis or active CNS lupus. Thus, use of the drug in these conditions is not approved. However, as more data becomes available, the recommendations will change. Adverse effect profile of belimumab is also favorable. In December 2019, GSK, the maker of belimumab, announced results of the BLISS-LN trial where belimumab was shown to be effective in reducing nephritis. However, the approval of belimumab for treatment of lupus nephritis is still pending.

Rituximab is an anti-CD20 antibody, which is an important drug in the treatment of rheumatoid arthritis, some malignancies, and some dermatological conditions. There have been many trials of rituximab in SLE also. The first few published studies were open, uncontrolled studies. For example, the data published by Leandro et al. in 2002 shows that there were improvements in both clinical and laboratory features of SLE after treatment with rituximab (500 mg; 2 doses, 2 weeks apart). This therapy was used along with oral steroids and i.v. cyclophosphamide. In 2006, Ng et al. published results of a trial using rituximab for refractory SLE. They showed that repeated cycles of rituximab may be helpful in difficult-to-treat lupus. However, most of these were clinical open studies. Later, two RCTs were undertaken to assess the efficacy of rituximab in lupus: LUNAR (renal lupus) and EXPLORER (non-renal). Both trials studied rituximab as an add-on therapy to the standard regimen of immunosuppressants like steroids. Overall, the EXPLORER trial did not reveal any extra benefit of rituximab when added to standard therapy. But subgroup analysis revealed significant effect on the primary end point in African-American and Hispanic patients. Also, there were significant fall in anti-ds-DNA levels and rise in complement levels. The dose of rituximab used was 1000 mg, 2 doses, 14 days apart. Oral steroid was also used in tapering doses. In the LUNAR trial, patients with Class III or IV lupus nephritis were randomized to receive rituximab as two 1000 mg doses, 14 days apart, to be repeated after 6 months. The primary end point of renal response at week 52 was not met. The only significant findings were, like EXPLORER trial, decrease in anti-ds-DNA and increases in complement levels. However, further analysis revealed that patients of African ancestry were more likely to respond to rituximab. Also, there was more reduction in proteinuria in the long term in the rituximab group. So, overall, both these trials were negative. So, although clinical results were encouraging, the randomized trial data did not support
the use of rituximab. This made the use of rituximab for SLE controversial. In 2019, a meta-analysis was published on this topic.\textsuperscript{27} Twenty-four studies were analyzed. It was seen that, overall, in controlled trials with rituximab, there was more probability of total remission (OR=2.02, 95% CI: 1.23–3.32, $P<0.01$). Also rituximab is associated with more decrease of proteinuria compared to controls. So, based on this meta-analysis, rituximab may be considered as a viable option in lupus nephritis. The ideal dose is still debated because some of these trials used four 375 mg/m$^2$ weekly doses and some used two 1000 mg fortnightly doses.\textsuperscript{28}

Another anti-CD20 therapy tried in clinical trials for SLE was \textit{Ocrelizumab} (OZM) (humanized antibody).\textsuperscript{28} There were two trials: BEGIN (non-renal) and BELONG (Renal). The BEGIN study was stopped early. In the BELONG trial, OZM was used at doses 400 mg or 1000 mg on days 1 and 15, and then 4 monthly.\textsuperscript{28} This trial was also stopped early due to increased risk of infections in the group receiving OZM+MMF. The intention-to-treat analysis at 32 weeks showed that there was some improvement in renal response in the OZM group, although it did not reach statistical significance. But the data also showed that there was more probability of response when OZM was combined with the \textit{Euro-Lupus} protocol. But as of now, OZM is not a priority candidate drug for lupus trials. The drug is only approved for some forms of multiple sclerosis.

\textit{Ustekinumab} (UKB) is an IL-12/23 antagonist.\textsuperscript{29} IL-12 is involved in activation of various T-cell subsets involved in autoimmune response. IL-23 is involved in expansion and survival of pathogenic Th-17 cells. These two pathways are closely related (\textbf{Fig. 2}). In September 2018, Vollenhoven et al. published a study of UKB in active SLE in the \textit{Lancet}.\textsuperscript{29} In this study, UKB was given intravenously at the beginning, followed by 90 mg subcutaneously every 8 weeks. Like other biologics, this was also given along with standard therapy. At 24 weeks, there was significantly more response with UKB, compared to placebo. The same group of researchers published a follow-up study in 2019.\textsuperscript{30} In this, it was shown that the benefits of UKB were maintained at 48 weeks. There were no excess malignancies or opportunistic infections. Presently, UKB is approved for Psoriasis, Ulcerative colitis, and Crohn’s disease. But in the future, this may be a promising therapy for active SLE.

\textbf{Baricitinib} is an oral Jak1 and Jak2 inhibitor, which has been approved for use in rheumatoid arthritis. Recently, there have been trials of baricitinib in SLE. In 2018, Wallace et al. published the results of a Phase II trial of baricitinib in SLE patients with arthritis or dermatological manifestations.\textsuperscript{31} Here, it was found that baricitinib significantly improved these manifestations at 24 weeks. Thus, this was a proof of concept that baricitinib can be a viable option for SLE patients in addition to standard therapy. However, the dose of baricitinib used (4 mg) has raised some concerns about the potential for serious side effects like neutropenia.\textsuperscript{32} A Phase 3 trial (\textit{SLE-BRAVE-X}) is underway to test the efficacy of baricitinib in SLE. This and similar other studies can clarify the role of this drug in the future.

**New Frontiers**

The most promising new target in controlling inflammation is the glucocorticoid pathway (\textbf{Fig. 3}).

\textit{Glucocorticoid-induced leucine zipper (GILZ)} is one of the GREs in the cell nucleus and it is one of the earliest areas in the DNA activated by the hormone.\textsuperscript{33} GILZ is one of the principal mediators of anti-inflammatory activity of GCs. The most robust evidence of the anti-inflammatory activity of GILZ is its effect on the NF-$\kappa$B/MAPK pathway.\textsuperscript{33} It directly inhibits NF-$\kappa$B and prevents induction of the
proinflammatory genes. Overall, it shifts the inflammatory milieu from Th1 to Th2 response. This molecule is encoded by the Tsc22d3 gene located on the X chromosome. In autoimmune diseases like SLE, it has been shown that active disease is associated with lower intracellular GILZ levels. This raises the possibility that GILZ deficiency is one of the factors in the pathogenesis of this disease and conversely, GILZ augmentation may be a potential therapeutic target. GILZ has effect on Th1, 17 cells and also B-cells. Deletion of GILZ in mouse models is associated with an increase in B-cells in blood. And increased B-cells means increased autoantibodies.

As discussed in the introduction section, glucocorticoids are associated with a lot of side effects and this raises a lot of problems in long-term treatment. So, it may seem like a paradox that the same glucocorticoid pathway is now the focus of research. But this new research is aimed at other intermediary compounds in that pathway which can maintain the immunosuppressive effects without giving rise to the side effects. So, there is a lot of research to find glucocorticoid receptor agonists and modulators, also called Selective Glucocorticoid Receptor Agonist & Modulator (SEGRAMs). GILZ is one such target to bypass the glucocorticoid receptor. It has good immunosuppressive activity and also, it lacks significant metabolic effects. It has neutral or even positive effect on bone density. However, all metabolic effects are still not known like its effect on glycemic status, skin thinning, or cataracts. So, although this is an exciting prospect, its potential for human use is still unknown. Research on GILZ till now is mostly animal model-based. Some studies have used truncated regions of the protein while others have used virus vectors with transcription factors to induce GILZ expression in laboratory animals. Presently, two SEGRAM compounds under investigation, RU24858 and ORG 214007-0, are based on targeting GILZ.

Other newer therapeutic options, which are in various stages of trial, are mentioned here:

- **Tabalumab**: Anti-BAFF monoclonal antibody; trials: ILLUMINATE-1 and 2
- **Epratuzumab**: Anti-CD22 antibody; trials: EMBODY 1 and 2
- **Atacicept**: Anti-TACI, tumor necrosis factor transmembrane activator and calcium modulator and cyclophilin ligand interactor; trials: ADDRESS-II; APRIL-SLE
- **Blisibimod**: Anti-BLyS antibody; trials: PEARL-SC
- **Rigerimod**: Peptide derived from a region of U1-70k snRNP protein; immunomodulator binding to MHC-II; can restore immune tolerance; Phase IIb trial encouraging; further trials in progress
- **Others**: IL-2 therapy, anti CD40 antibody etc.

**Conclusion**

As the earlier discussion makes clear, there are a lot of options in SLE management. Steroids are needed in the beginning and during life threatening flares. But once the patient is stabilized, we should try to shift to the steroid sparing therapies in order to avoid the long-term side effects. Choice of steroid-sparing agents or biologicals should be based on patient profile, affordability, and organ involvement.

**References**


Abstract

Gout or monosodium urate (MSU) crystal arthropathy is a disorder caused by hyperuricemia (serum urate >6.8 mg/dL [>0.4 mmol/L]) that results in the precipitation of monosodium urate crystals in and around joints, resulting into recurrent acute or chronic arthritis. Acute gouty arthritis is characteristically monoarticular and often involves the 1st metatarsophalangeal joint or ankle. Symptoms of gout include acute, severe pain, tenderness, warmth, redness, and swelling. Definite diagnosis requires demonstration of monosodium urate crystals in synovial fluid. This chapter deals with practical approach to diagnosis and management of patients with gouty arthritis.

“Gout is the Only Enemy That I Do Not Wish to Have at My Feet”
–Reverend Sydney Smith (1841)

Introduction

Gout is one of the oldest joint diseases known to humanity. The term gout originated from the word ‘gutta’ meaning a drop (in Latin), as the ancient belief was that the devil is causing the disease by instilling the poisonous humor into the joint of the victim drop by drop.

Gout is a crystal-deposition disease that results from chronic elevation of uric acid levels above the saturation point for monosodium urate (MSU) crystal formation. Normal level of serum uric acid (sUA) is 7 mg/dL in males and 6 mg/dL in females. Initial presentation is mainly severely painful episodes of peripheral joint synovitis (acute self-limiting “attacks”) but joint damage and deformity, chronic usage-related pain, and subcutaneous tophus deposition can eventually develop. Chronic recurrent gouty arthritis leads to development of tophi in the cartilage, tendon, or other soft tissues.

Epidemiology

The global burden of gout is substantial and seems to be increasing in many parts of the world over the past 50 years. Gout is most common inflammatory arthritis in men aged more than 50 years. Overall prevalence of gout in adult male is 1–2%. Prevalence in India is 0.1%, but incidence and prevalence have been doubled over past two decades probably because of adoption of western life styles. Gout is rarely seen in premenopausal females and children. After menopause, due to lack of estrogens, females are at equal risk of developing gout.

Pathogenesis

The disease often runs in families, but the genetic basis of gout is not well understood. Uric acid is the end product of purine degradation in humans. Purines are derived either from the diet or by de novo synthesis. Normal metabolism includes conversion of purine first into hypoxanthine in presence of enzyme xanthine oxidase, then hypoxanthine into xanthine again in presence of enzyme xanthine
oxidase, and finally xanthine is converted into uric acid which is a trioxypurine. Most of the uric acid is eliminated through urine or intestine, the kidney excretes two-thirds, and rest one-third is excreted via intestine.

**Classification**

**Primary Gout**
- Unknown cause
- Genetic defects in renal handling of urate
- Under secretors (90%) and overproducers (10%)

**Secondary Gout**
- Increased urate production:
  - Inherited enzyme defects (HGPRTase deficiency, glucose-6-phosphatase deficiency)
  - Myeloproliferative disorder
  - Psoriasis
  - Hemolytic diseases
  - Malignancies
  - High purine diet, alcohol
- Decreased renal clearance:
  - Renal: Chronic kidney disease, polycystic kidney disease, lead nephropathy
  - Endocrine: Hyperparathyroidism, hypothyroidism, diabetes insipidus
  - Metabolic syndrome: Obesity, hypertension, dyslipidemia
  - Drugs: Diuretics, low dose aspirin, pyrazinamide, ethambutol, cyclosporine
  - Others: Down syndrome, sarcoidosis, toxaemia of pregnancy

**Stages**
These are the following four stages of gout:
- Asymptomatic hyperuricemia
- Acute gouty arthritis
- Intercritical periods (asymptomatic)
- Advanced/chronic gout (frequent or constant joint pain, tophi)

**Asymptomatic Hyperuricemia**
Asymptomatic hyperuricemia is accidental finding and does not warrant urate lowering therapy. Whenever patient comes at this stage, meticulous search for other comorbidities must be done and it’s rewarding. Treatment of asymptomatic hyperuricemia should be done only in those patients who have history of kidney stones and asymptomatic patients with very high sUA, that is, more than 12 mg/dL in men and more than 10 mg/dL in women.

**Acute Gouty Arthritis**
In an acute presentation, patients will notice severe pain, redness, swelling, warmth, and severe tenderness in one or more joints. Symptoms worsen within first 24 hours. Joint involvement (in order of decreasing frequency) includes the metatarsophalangeal joint (podagra), forefoot, the ankle, the knee, the wrist, and the fingers. In elderly women, an initial presentation may be acute arthritis of fingers, having inflamed Heberden’s and Bouchard’s nodes. Untreated acute gout usually resolves within 1–3 weeks.

**Intercritical Gout**
This is the period between two attacks of gout. Approximately 60% of patients have a second attack within the first year, and 78% have a second attack within 2 years. Only 7% of patients do not have a recurrence within a 10-year period.

**Chronic Tophaceous Gout**
Tophaceous disease is more likely to occur in patients with the following: a polyarticular presentation, a serum urate level higher than 9.0 mg/dL, and a younger age at disease onset (i.e., 40.5 years or younger). The rate of tophi formation correlates with the duration and severity of hyperuricemia. The most common sites include the joints of the hands and feet. The helix of the ear, the olecranon bursa, and the Achilles tendon are classic, though less common, locations for tophi. Additionally, urate deposition in kidneys could lead to nephrolithiasis.

**Diagnosis**
- Clinical picture
- Crystal examination
- Serum uric acid
- Imaging

**Clinical Pictures**
Clinical features helpful in establishing provisional diagnosis of gout:
Gout Is the Only Enemy That I Do Not Wish to Have at My Feet

CHAPTER 215

- Rapidity (12–24 hours) with which inflammation reaches maximal
- **Location:** 1st MTP (most common), intertarsal areas, ankle, knee, insertion of tendoachillis, olecranon
- Monoarticular, intermittent arthritis
- Spontaneous and complete resolution with or without treatment
- Presence of visible or palpable lesion, which by location, texture, or appearance is likely to be tophus
- History of similar episodes in past
- A recent history of trauma, surgery, intercurrent medical illness, or initiation of urate lowering medication or other culprit medicines
- Presence of hyperuricemia

**Joint Aspiration and Synovial Fluid Analysis**

Identifying urate crystals in fluid aspirated from an affected joint is the only definitive way to diagnose gout. MSU crystals are needle-shaped and negatively birefringent on simple polarized light microscopy. In an acutely inflamed joint, these crystals are seen in polymorphonuclear cells.

**Hyperuricemia**

Hyperuricemia should never constitute a sole criterion for the diagnosis of gout as hyperuricemia is not present in 40% episodes at the time of acute attack.

**Imaging**

**Joint X-ray:** X-ray in gout shows typical punched out lesions with scalloping margins/rat bite erosions (Martel’s sign or G sign). These are asymmetrical, eccentric, and away from joint margins.

**High resolution ultrasound:** Detect subclinical Microtophi and MSU deposit within cartilage of 1st MTP Joint.

**MRI:** It shows bone “edema,” soft tissue pannus, and swelling.

**Management**

**Aims in the Management of Gout**

Maintain serum urate in non-tophus gouty arthritis patients less than 6.0 mg/dL and if chronic tophaceous gout then target serum urate level is less than 5 mg/dL to prevent future attacks and reverse prior damage (urate-lowering therapies).

**Non-pharmacological Management**

Life style modifications that are important in reducing risk for gout and/or reducing urate levels (Table 1).

**Pharmacological Treatment of Acute Gout**

**Guidelines**

- Affected joints should rest, fomentation should be done.
- Analgesic and anti-inflammatory drug therapy: commenced immediately and continued for 1–2 weeks.
- **Colchicine:** Effective alternative (preferably low-dose colchicine)

### TABLE 1 Life style modifications important for reducing the risk of Gout

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Management modality</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>Reduction in meat, sea food</td>
<td>Decreased risk</td>
</tr>
<tr>
<td></td>
<td>Increase in low fat dairy intake</td>
<td>Decreased risk</td>
</tr>
<tr>
<td></td>
<td>Increase in protein/complex carbohydrate</td>
<td>Decreased risk</td>
</tr>
<tr>
<td></td>
<td>Reduced fat</td>
<td>Decreased risk</td>
</tr>
<tr>
<td></td>
<td>Reduced beverages beer &gt; distilled spirits &gt; fruit juices &gt; and high fructose corn syrup containing soft drinks</td>
<td>Decreased risk</td>
</tr>
<tr>
<td>Obesity</td>
<td>Weight reduction</td>
<td>Decreased risk</td>
</tr>
<tr>
<td>Hypertension (HTN)</td>
<td>Reduce BP</td>
<td>Decreased risk</td>
</tr>
<tr>
<td>Culprit drugs</td>
<td>Substitute</td>
<td>Decreased risk</td>
</tr>
</tbody>
</table>
Urate-lowering drugs (Allopurinol/Febuxostat) should not be started during an acute attack. In patients already on Allopurinol/Febuxostat, it should be continued with simultaneous treatment for acute attack.

**Terminating the Acute Gout Flare**

Options: Virtually all anti-inflammatory agents have been used effectively in terminating acute gouty flare.²

**NSAIDs**

- Most useful agent is indomethacin in a dose of 50 mg 6 hourly for 2 days followed by 50 mg 8 hourly. Once pain settles, it can be reduced further to 25 mg 8 hourly. Other nonsteroidal anti-inflammatory drugs (NSAIDs) that can be used are naproxen (750 mg/day), etoricoxib (120 mg/day), and diclofenac (50 mg 8 hourly).
- NSAIDs are relatively contraindicated in patients suffering from renal diseases, peptic ulcer disease, congestive heart failure, and hypertension.
- Aspirin used for cardiovascular prophylaxis can be continued during acute attack under cover of anti-inflammatory agents.

**Colchicine**

Colchicine is the ideal drug where diagnosis of gout is not confirmed, the latest recommendation is to start 2 tablets of 0.5 mg colchicine as loading dose then 0.5 mg, 1 hour later, if needed, one more tablet of 0.5 mg after 12 hours, then continue colchicine in a dose of 0.5 mg twice or thrice a day after meals until acute attack resolves.¹²,¹³

**Corticosteroids**

Preferred only when NSAIDs or colchicine are contraindicating or ineffective especially useful in polyarticular gout following surgery, renal or hepatic insufficiency, or congestive heart failure.

*Intraarticular:* 40 mg of triamcinolone acetonide or 80 mg of depot steroid (methylprednisolone).

*Parenteral (intramuscular or intravenous):* Methylprednisolone (100–150 mg), the dose can be repeated 12 hourly for 1–3 days in incomplete responders.

*Oral:* 20 mg of prednisone BD, taper to stop within 7–10 days.

**ACTH (Adrenocorticotropic Hormone)**

*Dose:* Between 25 and 50 IU IM/SC; the dose can be repeated 12 hourly for 1–3 days in incomplete responders.

**IL-1β Inhibitors (Anakinra, Canakinumab, and Rilonacept)**

Highly effective but cost is the constrain.

**Gout Flare Prevention (Prophylaxis)**

*Aim:* To decrease frequency and severity of acute gout flares, especially when starting urate lowering therapy. Options:

- Oral colchicine (in dose of ≤0.6 mg twice daily after meals)
- NSAIDs-benefit not established but can be used in a patient who is intolerant or in whom colchicine is ineffective
- IL-1β inhibitors? (Rilonacept; canakinumab)

Prophylaxis is initiated when urate-lowering therapy is started and stopped when sUA is in goal range for more than or equal to 6 months.

**Management of Recurrent, Intercritical, and Chronic Gout**¹¹

*Goal of therapy:* sUA < 6 mg/dL

*Candidates for chronic therapy*

- Patients with two or more attacks per year
- Patients with tophi
- Patients with renal insufficiency
- Patients with uric acid stones

*Co-prescribe:* Colchicine or NSAIDs for 6 months

Avoid use of medications that can increase sUA. Example: diuretics, ethambutol, pyrazinamide, etc.

*Options:* Agents that promote uric acid excretion (uricosuric agents):

- Probenecid
- Sulfinpyrazone
- Benzbromarone
- Losartan
- Fenofibrate
- Vitamin C

Agents that inhibit uric acid formation (xanthine oxidase inhibitors):
Gout Is the Only Enemy That I Do Not Wish to Have at My Feet

CHAPTER 215

1379

- Allopurinol
- Febuxostat

Agents that convert uric acid to allantoin (uricase preparations):
- Rasburicase: Recombinant fungal uricase (Aspergillus flavus and Candida utilis)
- Pegloticase: Pegylated, recombinant, porcine-baboon uricase

Biologic Agents
- Anakinra
- Canakinumab
- Rilonacept
- Start uric acid lowering therapy 1–2 weeks after inflammation has settled
- Initial long-term treatment of recurrent uncomplicated gout (Allopurinol or febuxostat)

Uricosuric Agents

Promote uric acid excretion
- Hyperuricemia results from impaired renal uric acid clearance in 90% of gout patients (under-excretors of uric acid).
- Candidate patients for uricosurics are fewer than with xanthine oxidase inhibitors.

Limitations of uricosurics:
- Ineffective in renal insufficiency (CrCl < 50–60 mL/min)
- Results in modest decrease in sUA
- Risk of uric acid stone formation
- Cannot be used in presence of renal calculi

Probenecid: Achieve satisfactory control in 60–85% of patients and dose is 1–2 gm/day.

Sulfinpyrazone: It is uricosuric agent and related to phenylbutazone. It also acts as antiplatelet agent. Therefore, should be used cautiously in patients, who are anticoagulated, have bleeding problem and peptic ulcer disease.

The dosage is 100–200 mg twice a day and increase up to 800 mg/day.

Patients on uricosuric drugs are advised to maintain high urine flow (plenty of water intake) to avoid crystallization of uric acid in renal tubules.

Benzbromarone: Potent uricosuric drug used in patients with no improvement with allopurinol and in renal transplant patient. It is safe in mild to moderate renal impairment and rarely cause hepatotoxicity. Therefore SGOT/SGPT level should be monitored before starting and after continuation of therapy.

Dosage is 50–200 mg daily.

Angiotensin receptor blocker: Particularly losartan is also uricosuric drug and acts by inhibiting renal tubular reabsorption of urate.

Fenofibrate: It is a lipid lowering agent and has uricosuric effect.

Vitamin C: It can be given in a dose of 8 gm/day in divided dosage.

Urate-lowering Strategies

Inhibit uric acid formation by inhibiting xanthine oxidase inhibitors:
- Allopurinol
- Febuxostat

Allopurinol: Approved at daily doses of 100–800 mg/day but 95% of dosing is at less than or equal to 300 mg/day and at this dose it sub-optimally controls the sUA levels (only 21–55% patients achieve target sUA of 6 mg/dL).

Factors contributing to low dosing of allopurinol:
- Intolerance (~10%) including rare but life-threatening rashes and hypersensitivity syndrome.
- Dosage reduction recommended with impaired renal function.
- Minimal RCT evidence for safety and efficacy of allopurinol at doses more than 300 mg/day.

Unmet needs with Allopurinol therapy:
- Under-dosing: Only 53% patients achieve target sUA with the commonly used dose of 300 mg/dL.
- Intolerance and allergies: Drug rash with Eosinophilia and Systemic symptoms (DRESS)
- Dosing adjustment required in comorbid conditions: Kidney impairment
- Drug: Drug interactions (Azathioprine, Mercaptopurine)

The above factors result into non-compliance (50%) and treatment failure.

Febuxostat: Non-purine, selective xanthine oxidase/xanthine dehydrogenase inhibitor, which completely inhibits activity of XO enzyme by obstructing substrate binding.
Indications
- Chronic management of hyperuricemia in patients with gout
- Allopurinol hypersensitivity/intolerance/failure
- CKD, where the reduced allopurinol dose sub-optimally controls the sUAc levels
  Initiate dose is 40 mg OD. Monitor the sUAc after 2 weeks. If target (<6 mg/dL) not achieved, shift to the higher dose (80 mg or 120 mg).

Adverse effects: Transaminitis, acute gouty flares, myocardial infarction, immune hypersensitivity reaction, renal failure, angioedema.

Uricase
- Apes and human beings lack uricase
- Uricase converts insoluble uric acid into soluble allantoin

Recombinant Uricase
Rasburicase: Short-term use in tumor lysis syndrome but unsuitable in gout due to short half-life and immunogenicity.

Pegloticase: It is useful in treatment failure cases and tophi. Dose 8 mg IV every 2 weeks. Limitation is infusion reactions, attenuation of clinical response due to development of inhibitory antibodies.

Conclusion
Hyperuricemia and gout are not synonymous. Do not treat asymptomatic hyperuricemia. At least half of patients who present with an initial attack of gout take a diuretic or other medication predisposing to hyperuricemia or gout. Do not start a urate-lowering agent during an acute attack of gout; however, do not stop one if the patient is already taking it and experiences a recurrence. Limiting allopurinol to 300 mg/day is insufficient to control gout in many cases; aim should be “dose to target.” Febuxostat represents an effective treatment option to allopurinol may be considered as first-line treatment. Biologics are very effective option, but cost is the main constraint.

References
There is an increased risk of nonalcoholic fatty liver disease (NAFLD) in patients with rheumatoid arthritis (RA) as they share a lot of risk factors. Methotrexate (MTX), which is used in the treatment of RA, further increases the risk as it is a potentially hepatotoxic drug. NAFLD related to MTX is believed to be related to folate antagonism and genetic (C677T) polymorphism. However, there is an absence of significant clinical and histological hepatic worsening seen. Possible options for monitoring include LFT, USG, Fibroscan, and scoring systems (like NAFLD-LFS). Transaminase elevations more than three times the normal values are rarely seen. If at all seen, then the first step should be to evaluate for other confounding causes. If MTX is the likely culprit, it should be withheld and restarted after normalization of values. As a last resort, other DMARDs can be tried; however, it should always be the priority to keep the patient on MTX for as long as possible as it is the sheet anchor drug in RA. Also, MTX is associated with a possible reduction in serious outcomes and has a possible protective effect from the development of metabolic syndrome.
be a reason for this discrepancy in the actual prevalence. However, the simultaneous use of other disease-modifying antirheumatic drugs (DMARDs), viz. hydroxychloroquine and sulfasalazine, does not influence the development of NAFLD with transaminitis. In another Indian study involving patients with RA on low-dose weekly MTX, only 7.5% were reported to have significant hepatic fibrosis as assessed by transient elastography. There is a paucity of Indian studies regarding the exact prevalence of NAFLD (by USG) in patients with RA and on MTX.

**Role of MTX in Pathogenesis**

As per the studies conducted in the past, the duration of MTX therapy and especially its cumulative dose seems to be significantly related to the occurrence of transaminitis. However, some also suggest that these factors are not significant in causing transaminitis in patients with RA.

NAFLD associated with MTX therapy is believed to be related to folate antagonism in the hepatic tissues which have high cellular turnover. The probable mechanism involves inhibition of purine metabolism, polyamine synthesis, and homocysteine metabolism. The liver biopsy specimens taken from the patients with RA have demonstrated hepatic folate deficiency and accumulation of MTX-polyglutamates in the liver. The other culprit mechanism is related to the genetic polymorphism in metabolic pathways of MTX that resulted in the development of NAFLD. It is also been reported that C677T polymorphism increases the likelihood of MTX toxicity. However, studies with new grading systems and electron microscopy now have confirmed an absence of significant changes in liver histology in patients with RA on long-term MTX. There is also an absence of clinical meaningful hepatic worsening. Hence, it is safe to use MTX for a long duration with proper monitoring in patients with RA. In fact, many of the serious adverse effects of MTX are linked with the daily dosing or very higher doses (e.g., 100 mg/week) that was used in the past but with the introduction of lower and less frequent dosing regimens, these toxicities are hardly seen nowadays.

**Does MTX have a Protective Role?**

It is seen that the patients with RA on MTX, despite having minor or major transaminitis, do not have an increased risk of liver cell failure, cirrhosis, or death. There is a strong trend toward less of these serious outcomes in them although not reaching the statistical significance. However, the reason for this possible decrease in serious outcomes is not completely apparent. Similarly, a negative association between MTX use and the presence of the MS is noted, which suggests that MTX may protect against its development. This protective effect of MTX is not a result of generic anti-inflammatory effect, but is likely to be drug-specific. This is not observed with any of the other DMARDs. A similar association was also observed in another study where it was assumed to be purely due to the anti-inflammatory effect of MTX, although no data was presented to support it. The lower incidence of MS in patients on MTX may be seen because of the increased physical activity in these individuals as the disease activity reduces with appropriate treatment; however, further studies are needed to confirm this postulate.

**Clinical Features**

Patients with RA and NAFLD are structurally obese with clinical evidence of insulin resistance in the form of acanthosis nigricans. They are usually asymptomatic but may have occasional pain in the right upper quadrant of abdomen due to underlying hepatomegaly. Clinical features due to enzyme derangements in the form of loss of appetite, nausea, or vomiting are minimal because the degree of transaminitis is generally minimal despite the usage of MTX. Peripheral stigmata of chronic liver disease and portal hypertension may be rarely seen in advanced cases (especially those with cirrhosis).

**Diagnosis**

Since the diagnosis of NAFLD does not require any invasive testing, it is always to be done by history, physical examination, liver imaging, and few blood tests (to exclude other liver diseases). History of ethanol consumption of more than 20 g/day in men and more than 10 g/day in women exceed the diagnostic cut-off for NAFLD. Intake of medications causing hepatic steatosis and other causes of liver injury like viral hepatitis, autoimmune diseases must be excluded. Suspicious drugs including other co-prescribed hepatotoxic drugs in the treatment of RA like leflunomide and NSAIDs and other risk factors for NAFLD like obesity, diabetes, dyslipidemia, insulin resistance, and MS may also increase the likelihood of NAFLD and they always need careful evaluation. Hence,
it is not easy to simply mark the liver dysfunction to MTX in patients with RA.

Liver biopsy is the gold standard to confirm NAFLD, but it is an invasive procedure and is very rarely advocated for the confirmation of MTX related liver disease. It is rather indicated for the evaluation of other potential causes of transaminase elevations when the diagnosis is unclear. A pretreatment liver ultrasound for patients at a high risk of NAFLD is recommended. Some centers even advocate a pretreatment liver biopsy for high-risk patients but is not recommended as a blanket practice in current guidelines. Amongst the imaging modalities, ultrasonography of the liver is the imaging modality of choice for screening of fatty liver. This has almost replaced the liver biopsy for the diagnosis of NAFLD. Another imaging technique is the Transient Elastography or Fibroscan, which measures liver fibrosis by measuring liver stiffness. The other newer imaging modalities like Shear-Wave Elastography (SWE), Proton Magnetic Resonance Spectroscopy (¹H-MRS), MRI using Proton Density Fat Fraction (MRI-PDFF), and MRE (MR Elastography) are also useful in diagnosis.

Biochemical tests include estimation of alanine transaminase (ALT) and aspartate transaminase (AST) levels in serum. Elevation of ALT and AST is very modest and usually less than twice normal. As the hepatic fibrosis increases, the ALT levels fall further downward. The characteristic AST to ALT ratio of less than 1 seen in NASH patients reverses as the disease progresses toward cirrhosis. Another biochemical test is the detection of Cytokeratin/Keratin (CK/K) 8 and 18 fragments in blood, which can help to differentiate NASH from simple steatosis or normal liver more reliably than serum aminotransferase levels.

Many other noninvasive scoring systems can also be very useful. The FIB-4 score, for instance, is a valuable tool to diagnose liver disease in patients with RA treated with long-term MTX therapy. Hepatic indices like NAFLD-Liver Fat Score (NAFLD-LFS), Hepatic Steatosis Index (HSI), Fatty Liver Index (FLI), and Aspartate aminotransferase-to-Platelet Ratio Index (APRI) are handy and easy tools and can also reliably predict NAFLD. The Lipid Accumulation Product (LAP) is also useful to identify people with hepatic steatosis. Out of the four NAFLD prediction scores—FLI, HSI, LAP, and NAFLD-LFS; it is found that the NAFLD-LFS score has the best noninvasive prediction value for NAFLD.

### Treatment

The treatment of patients on MTX having abnormal liver functions is always debatable. The first step in the treatment of such patients is to confirm the diagnosis. Evaluation for other potential causes, viz. NSAIDs, alcohol intake, obesity, and viral infections (hepatitis B and C), should be done. If no other cause is identifiable, then look at the degree of transaminitis. Though transaminase elevations do not necessarily correlate with the stage of NAFLD, most of the guidelines have used this to monitor hepatotoxicity with MTX. The estimation of baseline transaminase levels before MTX initiation is important. A person who previously had elevated transaminase levels which has not changed after starting MTX should not be subjected to further evaluation. Transaminase elevation more than three times the upper limit of normal is often an indication to withdraw the drug. In case of persistent low-grade elevations particularly if the trend is for a progressive increase in the levels, the dose of MTX is reduced and further investigations are carried out simultaneously. Some also advise stopping MTX when transaminases rise to more than two times the upper normal limit. However, irrespective of the cut-off used, it may be restarted at a lower dose after normalization of these levels. Some other modalities like USG of the liver, Fibroscan, and Scoring Systems (FIB-4 Score) can also be used to identify NAFLD and adjust the MTX dose accordingly. Now, the question that still remains unanswered is—“What if significant transaminitis reappears even with lower doses of MTX and other causes being ruled out?”. Here, we would like to suggest switching to other DMARDs or biologicals after considering the patient’s disease severity, accessibility, and affordability. However, we need to remember that MTX is still the sheet anchor drug in RA with probably being the most efficacious, cheapest, easy for compliance, and with minimal side effects (especially at a dose less than 25 mg/week, which is far lower than the doses used in oncology) and its substitution should only be done if we are left with no options to continue with it.

### Conclusion

MTX is a proven culprit causing liver dysfunction in patients with RA, although with the current data and studies available, it is seen in very few patients. It is mostly transient and not always...
clinically significant enough to warrant its discontinuation. To exclude the other causes of NAFLD should be the first rule. Pharmacogenetic approaches may help to optimize the treatment with MTX but this may not be feasible in all parts of the world before starting this drug. Fibroscan is not available at all the diagnostic centers and the poor people of developing countries like India cannot go for repeat evaluations. At the most, what we can use for serial monitoring are LFTs, noninvasive scores (NAFLD-LFS), and occasional USGs of the liver for serial evaluation of such patients. MTX is and will always remain the gold standard backbone therapy in RA, and hence we recommend continuing therapy and keeping such patients on a regular follow-up to pick up liver dysfunction early. Careful small dose adjustments should be done as per the laboratory parameters and prompt reintroduction of the drug should be done as soon as the picture normalizes. To summarize the protective effect of MTX, it is associated with a possible reduction in serious outcomes and also has a possible protective effect from the development of MS.

References

1. John A. Incidence and factors associated with the development of non alcoholic fatty liver disease (NAFLD) among patients with rheumatoid arthritis [Internet]. Walden University; 2016. Available from https://scholarworks.waldenu.edu/dissertations/1972
Liver Dysfunction and NAFLD in RA: Is MTX Really a Culprit?


CHAPTER

217

Sexual Dysfunction in Rheumatic Diseases

Vinod Ravindran

Abstract

Normal sexual function is an important component of both physical and mental well being. Sexual dysfunction, therefore can negatively impact an individual’s quality of life. Sexual dysfunction, though not uncommon, remains an under-explored area in Rheumatology. There are several unique factors contributing to the burden of sexual dysfunction in patients with rheumatic diseases. This review discusses pertinent areas which need specific exploration and offers some thoughts on how to effect the therapeutic aspects of management of this challenging comorbidity in day-to-day rheumatology practice.

Introduction

Sexual health has been defined by the World Health Organization (WHO) as a state of physical, mental, and social well-being in relation to sexuality and it has been recognized as an important factor having positive or negative effects on an individual’s quality of life. The WHO has recognized sexual health as extremely important necessitating well thought out plans to pick them up, start preventive measures and appropriate management. Sexual functioning is a neglected area of quality of life in patients with rheumatic diseases and is not routinely addressed. In a study assessing the impact of an outpatient based intervention to improve rheumatologists’ identification of sexual health aspects in younger individuals with chronic rheumatological diseases found that only few rheumatologists ever screen their patients for sexual activity. Existing health assessment questionnaire and other quality of life tools for rheumatological conditions do not assess sexual function. Box 1 lists some of the barriers in effective exploration of the sexual dysfunction.

Female preponderance of several rheumatic diseases is an additional factor which may negatively impact effective communication between not only female patient-male clinician but also between female patient-female clinician. In addition, generally, cultural, religious and social barriers in India make the due assessment of sexual dysfunction difficult, irrespective of the gender. Shame and frustration prevent patients to volunteer the information on issues with sexual function. In addition, lack of specific exploration of this area by clinicians leads to under diagnosis of sexual dysfunction in such patients.
The Sexual Response Cycle

Sexual function and the amount of satisfaction derived from it have the potential to positively or negatively impact on the individual’s quality of life. Sexuality encompasses the sexual act itself, self-image and the valorization of self and the relationship with the partner. The sexual response cycle is comprised\(^6\)–\(^8\) of four distinct stages namely, desire, excitation, orgasm, and resolution. In either gender it leads to simultaneous and often reciprocal physiological changes allowing and facilitating the sexual act and its desirable outcomes. Any disturbances in sexual desire and physiological aspects of the sexual response cycle may cause distress and inter-personal difficulties and are labeled as sexual dysfunction.\(^8\)

Mechanisms of Sexual Dysfunction in Rheumatic Diseases

Sexual dysfunction in rheumatic diseases is fairly common ranging from 36% to 70%.\(^9\)–\(^11\) The factors responsible for aberration in the sexual function in rheumatic diseases can be categorized into physical and physiological domains (Table 1). In chronic rheumatic diseases both these domains are likely to play a part. Conditions such as osteoarthritis, ankylosing spondylitis and rheumatoid arthritis may prevent attaining relevant sexual positions. Both primary and secondary Sjogren’s syndrome can lead to vaginal dryness, which may cause dyspareunia. Pain and fatigue which are a part and parcel of many rheumatic diseases also contribute. Altered body image and apprehension about partner’s interest (for example, due to skin involvement in systemic sclerosis, psoriatic arthritis, and lupus or deformities of rheumatoid arthritis) may compound the problems. In some conditions such as ankylosing spondylitis erectile dysfunction has not only been reported to be common but appears linked to high disease activity.\(^12\)

Drugs and Sexual Dysfunction

Pharmacological treatment of the rheumatic diseases fortunately does not cause major issues as far as the sexual function is concerned. There are reports though of reversible erectile impotence caused by methotrexate, sulfasalazine, and hydroxychloroquine. Commonly used non-steroidal anti-inflammatory agents such as diclofenac, misoprostol, and naproxen may cause interference with libido. Antidepressant medications used in the management of fibromyalgia can lead to loss of desire and difficulty with orgasm. Steroids can contribute to sexual dysfunction in multiple ways including weight gain, abnormal hair growth, altered body image, psychosis, and striae.\(^13\)

Determinants of Sexual Dysfunction

Factors such as severity of the disease, levels of fatigue, amount of pain, physical limitations, act of weight bearing leading to discomfort, perception of self, self-esteem and emotional status, adverse effects of pharmacologic agents, effects of surgery, and fatigue either alone or in combination can determine the sexual function in an individual with rheumatic disease.\(^14\) Generally speaking, irrespective of the gender of the patient, sexuality is adversely impacted by level of pain, depression, and physical limitations. A recent study looking into sexual functioning and its correlates in premenopausal married Indian women with SLE found that dose of glucocorticoids, active lupus, presence of depression and anxiety, and marital satisfaction were all important determinants.\(^15\)

Strategies to Manage Sexual Dysfunction

General Measures

Irrespective of the type of rheumatic diseases, some practical tips to patients and partners are useful and easily adoptable (Box 2). They are generally aimed at relaxation, relieving pain and improving function. A useful resource in this regard is a booklet entitled “Sex and Arthritis” by the

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Contributors to sexual dysfunction in rheumatic diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical domains</td>
<td>Psychological domains</td>
</tr>
<tr>
<td>• Heightened tactile sensitivity</td>
<td>• Diminished sense of sexual attractiveness</td>
</tr>
<tr>
<td>• Reduced endurance</td>
<td>• Reduced sexual desire</td>
</tr>
<tr>
<td>• Impaired motion</td>
<td>• Reduced satisfaction</td>
</tr>
<tr>
<td>• Vaginal dryness</td>
<td>• Issues with sexual arousal</td>
</tr>
<tr>
<td>• Inability to have an orgasm</td>
<td>• Impaired sensation of penile turgidity</td>
</tr>
<tr>
<td>• Inability to have erection</td>
<td>• Inability to achieve orgasm</td>
</tr>
</tbody>
</table>
UK based charity Arthritis Research UK. This booklet has information on sexual positions which most couples can try and improve with a little experimentation and open discussion, and adopt positions that are comfortable and enjoyable for both partners.

### Specific Approaches

Panush and colleagues have proposed a specific multidisciplinary approach to manage sexual dysfunction entitled “PLISSIT” (for Permission, Limited Information, Specific Strategies and Intensive Therapy). Details of this approach have been provided in Table 2. It is envisaged that an ideal team would have psychologist, physiotherapist, occupational therapists, sex therapist, rheumatologist, and gynecologist.

It is also important to consider hip or knee arthroplasty as per the clinical needs. Both knee and hip arthroplasty have been shown benefit in improving sexual function mainly by allowing the liberty to choose a greater variety of sexual positions.

### Conclusion

Sexual dysfunction in rheumatic diseases is though common, remains either under or undiagnosed and affect men as well as women. It is important for the clinicians to be aware of this important aspect of their patients’ well-being and be prepared to explore it further and offer appropriate management with the help of a multidisciplinary team.

### References

Abstract

Autoimmune rheumatic diseases (ARDs) are multiple; diagnosis of these diseases depends on meticulous history, physical examination, and investigations. These diseases are characterized by inflammation, autoimmunity, and the presence of autoantibodies. Inflammation is assessed by acute phase reactants, viz. high leukocyte count, erythrocyte sedimentation rate, C-reactive protein, ferritin, alkaline phosphatase, and by low albumin levels. Various antibody tests are done to support the clinical diagnosis of ARDs, e.g., rheumatoid factor (RF), antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), etc. Positivity does not always confirm the diagnosis as false positivity may be seen in normal persons, in non-rheumatic diseases and other ARDs, e.g., ANA may be positive in rheumatoid arthritis (RA) patients and RF may be present in systemic lupus erythematosus (SLE); therefore, clinical setting and pre-test probability have to be considered before ordering or interpreting positive tests. Few patients may be suffering from ARD, but the tests may be negative. Therefore, a good correlation between clinical features and laboratory tests has to be done before the final diagnosis.

Introduction

Rheumatic diseases are multiple and are characterized by inflammation, autoantibodies and damage to the organs. To evaluate autoimmune rheumatic diseases (ARDs) it is very important to elicit a good detailed history and perform meticulous examination of patient before getting tests done. Ordering an "Arthritis Panel" should be avoided as tests of inflammation are non-specific and may be elevated in other conditions also. Similarily autoantibodies may be falsely positive in normal persons and in patients with non-rheumatic diseases. One antibody may be present in other ARDs too, for example, rheumatoid factor (RF) and antinuclear antibody (ANA).

Tests to Assess Inflammation

In response to inflammation there is increase in serum concentrations of acute phase reactants (APRs) (Table 1), for example, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, and alkaline phosphatase. Negative APRs are also there, which decrease with inflammation, for example, albumin.

ESR—ESR increases with age, upper limit for males is half the age while in females half of sum of age plus 10 (so for 70 year male it is 35 while in female will be 40).1 ESR is also high in anemia, infections, cancer, pregnancy, trauma, kidney disease, obesity, and with high fibrinogen levels. Its rise and fall may be delayed with the onset and remission of inflammatory disease, respectively.

CRP—It is more consistent than ESR as it rises and falls quickly. It gets elevated within 4 hours of inflammation or infections and peaks at 24–72 hours. In systemic lupus erythematosus (SLE) CRP is usually normal except in presence of infection, severe serositis, or synovitis.

Autoantibodies

Rheumatoid Factor (RF)

It is an autoantibody directed against the Fc (constant) region of the IgG molecule. Antibody may be of various
isotypes, IgM, IgG, and IgA. IgM RF is routinely measured using latex agglutination while all the three isotypes are measured using nephelometry and enzyme linked immunosorbent assay (ELISA). RF is present in 70–80% patients of RA. Titer usually correlates with the severity of rheumatoid arthritis. RF may be present in normal persons and in various other rheumatic diseases (Sjögren syndrome 75–95%, Mixed cryoglobulinemia type II 100%, SLE 15–35%, mixed connective tissue disease 50–60%, Systemic sclerosis 20–30% ANCA associated vasculitis, Dermato-/polymyositis 20%, Systemic vasculitides 5–20%, etc. and in non-rheumatic conditions as well (Table 2).  

**Anti-citrullinated Peptide Antibody (ACPA)**

It is an antibody against citrullinated peptide (post-translationally modified citrulline). It is better test for RA as compared to RF as it is 98% specific for RA but its sensitivity is equal to RF; that is, 70–80% and it is costly.

Seroprevalence of ACPA was found in 10% of other rheumatic diseases and in non-rheumatic diseases. Presence of ACPA may antedate RA by several years and is indicative of severe erosive disease.

**Antinuclear Antibody (ANA)**

The term antinuclear antibody describes a variety of autoantibodies that react with multiple intracellular antigens such as nuclear antigens (DNA, histone, nucleosomes, centromere, topoisomerase, etc.) and in some patients against cytoplasmic antigens (e.g., Jo1 or histidyl tRNA synthetase, mitochondria, smooth muscle cell, etc.).

ANA should be done by indirect immunofluorescent assay (IIFA) using human epithelial cells (HEP2) derived from human laryngeal carcinoma cell line as substrate. It is reported positive in 1: 80 or more dilution, depending on the kit manufacturer’s recommendations. ANA may be positive in 20% of normal sera, majority of which are against dense fine speckled 70 antigen (DFS-70). Anti-DFS antibody may be diagnosed by immunoabsorption...
method, which is seen in normal persons with false-positive ANA (Flowchart 1).^4

ANA should always be ordered when there are clinical features of connective tissue disease like fever, photosensitivity, alopecia, mucosal lesions, serositis, nephritis, Raynaud’s phenomenon, inflammatory polyarthritis, skin ulcers, skin rashes, sicca symptoms, and proximal muscle weakness. It should never be repeated once it is positive in significant titers.

ANA detection by ELISA: It is of low sensitivity so is not a preferred method for detection of ANA. The titer of ANA is more important than the pattern (Figs. 1A to C).

It may be positive in many autoimmune diseases and in diseases other than systemic rheumatic disease (Table 3).

**Extractable Nuclear Antigen (ENA) Profile (Table 4)**

If features of connective tissue disease (CTD) are present and ANA by IIFA is positive then the ENA profile should be ordered by Immunoblot or Line immunoassay (LIA) or by ELISA. ENA profile may be done in suspected Sjogren syndrome and inflammatory myositis even if ANA is negative.

- **Anti-dsDNA:** There are three methods of assessment:
  - IIF using crithidia Luciliae—It uses unicellular hemoflagellate, staining of its kinetoplast is seen with serial dilutions of plasma by IIF technique.
  - ELISA—Since titers are available by this method, so it is good for monitoring disease activity. Specificity for SLE by this method is 70%.^5 It also correlates moderately well with active nephritis.
  - Radioimmunoassay assay (Farr Assay)—Seldom used because of difficulty in disposing of radioactive material.

- **Anti-Sm and Anti-U1 RNP:** Both antibodies produce coarse speckled pattern (Fig. 1B) in IIF assay and corresponding antigens (Sm and U1 Ribonucleoprotein) colocalize in small nuclear ribonucleoprotein particles (sn RNP). Anti-Sm Ab is found in 20–30% patients of SLE and is specific for SLE unlike anti-dsDNA, it may remain positive in remission also. Anti-U1 RNP is present in all patients of mixed connective tissue disease (MCTD) and few patients of SLE (Table 4).

- **Anti-Ro (SSA) & Anti-La (SSB):** Autoantigen Ro60 is localized to nucleus and nucleolus, while Ro52 is localized to cytoplasm. So, if Anti-Ro52 (in cytoplasm) is present ANA may be reported negative by HEP2 IIF method. Anti-Ro52, if present in juvenile idiopathic inflammatory myositis (IIM) it denotes severe disease. In adults IIM Anti-Ro52 may be associated with ILD. The presence of Anti-Ro antibody in pregnant lupus patient may lead to congenital heart block, neonatal lupus syndrome in fetus and may be present in ANA negative lupus patients and may antedate SLE by 4 years. It may also be positive in subacute cutaneous lupus erythematosus.

  Anti-La/SSB autoantigen is present in both nucleus and cytoplasm but it is predominantly found in the nucleus. Anti-Ro and Anti-La Ab should be ordered when sicca symptoms or salivary gland enlargement is present and in SLE patients who wish to become pregnant.

**Anti-Neutrophil Cytoplasmic Antibody (ANCA)**

This is done by high-quality ELISA (more specific) or IIF (more sensitive but subjective).

ELISA: Current consensus is that in suspected ANCA associated vasculitis (AAV) first high-quality antigen...
specific ELISA test should be done if it is negative and clinical suspicion is strong, then repeat testing may be done by ELISA or IIF.\(^7\)

Specific ELISA tests for antibodies using purified specific antigens proteinase 3 (PR3) and myeloperoxidase (MPO) are associated with higher specificities and positive predictive value than IIF assays. Anti-PR3 ANCA is present in granulomatosis with polyangiitis (GPA) and Anti-MPO ANCA is present in microscopic polyangiitis (MPA). ANCA against both PR3 and MPO is seen in levamisole adulterated cocaine users.

**ANCA by IIFA (Figs. 2A and B)**

Using alcohol-fixed buffy coat leukocytes, there are two patterns.

- **Cytoplasmic ANCA (c-ANCA) (Figs. 2):** There is coarse granular staining of the cytoplasm. The main antigen is PR3, c-ANCA is seen in 90% cases of GPA (10% cases of GPA have ANCA against MPO antigen) and has greater specificity than p-ANCA. In limited GPA c-ANCA may be absent.

- **Perinuclear ANCA (p-ANCA) (Figs. 2A and B):** ANCA is directed against MPO antigen (occasionally against PR3). There is staining of the perinuclear area leaving cytoplasm clear. ANA positive patients may be falsely labeled as p-ANCA positive, this can be avoided if IIFA tests are done with both formalin and ethanol fixed substrates. p-ANCA is associated with MPA (90%), renal limited vasculitis (75–80%), eosinophilic granulomatosis with polyangiitis with renal involvement, drug induced AAV and ulcerative colitis.

- **Atypical ANCA:** The atypical patterns are usually confused with p-ANCA patterns and may be seen in
immune-mediated diseases such as CTD, inflammatory bowel disease, and autoimmune hepatitis. ELISA test for PR3 or MPO is negative.

Indications for getting ANCA done:
- Glomerulonephritis, especially rapidly progressive glomerulonephritis
- Pulmonary hemorrhage, especially pulmonary-renal syndrome
- Cutaneous vasculitis with systemic features
- Multiple lung nodules
- Chronic destructive disease of the upper airways
- Long-standing sinusitis or otitis
- Subglottic tracheal stenoses
- Mononeuritis multiplex or other peripheral neuropathy
- Retro-orbital mass
- Scleritis

Facts about ANCA:
- Negative test does not exclude the diagnosis of AAV, sometimes biopsy is required to confirm the diagnosis.
- Positive test does not establish the diagnosis of AAV as false positive may be seen in other diseases.
- Titers do not correlate with severity so disease should be assessed clinically.

Anti-phospholipid Ab (APLA)
Commonly three APLA are being done.
1. Lupus anticoagulant (LAC):
   Screening tests:
   - dilute Russell viper venom time (dRVVT)
   - activated Partial Thromboplastin Time (aPTT) is prolonged and fails to get corrected when the patient’s plasma is mixed with normal plasma excluding coagulation factor deficiency.

---

**TABLE 3** Diseases associated with a positive ANA

<table>
<thead>
<tr>
<th>Devices associated with a positive ANA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic autoimmune diseases</strong></td>
</tr>
<tr>
<td>SLE</td>
</tr>
<tr>
<td>Active 98–100%</td>
</tr>
<tr>
<td>Remission 90%</td>
</tr>
<tr>
<td>Scleroderma 95%</td>
</tr>
<tr>
<td>Rheumatoid arthritis 45%</td>
</tr>
<tr>
<td>Sjögren's syndrome 60%</td>
</tr>
<tr>
<td>Mixed connective tissue disease 100%</td>
</tr>
<tr>
<td>Drug-induced LE 80–95%</td>
</tr>
<tr>
<td>Raynaud's phenomenon 40%</td>
</tr>
<tr>
<td>Polymyositis/dermatomyositis 35%</td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis 15–40%</td>
</tr>
<tr>
<td><strong>Organ-specific autoimmune diseases</strong></td>
</tr>
<tr>
<td>Hashimoto's thyroiditis 50%</td>
</tr>
<tr>
<td>Graves' disease 50%</td>
</tr>
<tr>
<td>Autoimmune hepatitis 70%</td>
</tr>
<tr>
<td>Primary biliary cirrhosis 50–70%</td>
</tr>
<tr>
<td><strong>Infectious diseases</strong></td>
</tr>
<tr>
<td><strong>Viral:</strong> EBV, HIV, HCV, Parvovirus B19</td>
</tr>
<tr>
<td><strong>Bacterial:</strong> Subacute Bacterial Endocarditis, Syphilis</td>
</tr>
<tr>
<td><strong>Malignancies:</strong>* Lymphoproliferative diseases, Paraneoplastic syndromes</td>
</tr>
<tr>
<td><strong>Miscellaneous diseases:</strong>* Inflammatory bowel disease, Idiopathic pulmonary fibrosis</td>
</tr>
</tbody>
</table>

SLE, systemic lupus erythematosus; EBV, Epstein-Barr virus; HCV, hepatitis C virus; *Although positive tests of ANA are reported in these diseases more often than in healthy controls, precise estimates vary.

Source: Reproduced with permission from Reference 12.
TABLE 4

<table>
<thead>
<tr>
<th>ENA antigen</th>
<th>Antibody</th>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double stranded DNA</td>
<td>Anti-dsDNA</td>
<td>95% Specific for SLE + in active disease &amp; with nephritis</td>
</tr>
<tr>
<td></td>
<td>Anti-Sm Ab</td>
<td>Present in 10–20% SLE</td>
</tr>
<tr>
<td></td>
<td>Anti-Histone Ab</td>
<td>+ in drug induced lupus</td>
</tr>
<tr>
<td></td>
<td>Anti-Ribosomal Ab</td>
<td>Specific for SLE esp. neuropsychiatric lupus</td>
</tr>
<tr>
<td>Smith Ag</td>
<td>Anti-dsDNA</td>
<td>Present in 10–20% SLE</td>
</tr>
<tr>
<td></td>
<td>Anti-Sm Ab</td>
<td>+ in drug induced lupus</td>
</tr>
<tr>
<td></td>
<td>Anti-Histone Ab</td>
<td>Specific for SLE esp. neuropsychiatric lupus</td>
</tr>
<tr>
<td>Ribosomal P protein</td>
<td>Anti-Ribosomal Ab</td>
<td>Specific for SLE esp. neuropsychiatric lupus</td>
</tr>
<tr>
<td>Ro/SSA-Ro60 (protein of cytoplasmic RNA) &amp; Ro52 (ubiquitin ligase in cytoplasm)</td>
<td>Anti-Ro/SSA (Anti-Ro60 &amp; anti-Ro52)</td>
<td>+ in Sjögren syndrome 40–95% and in ANA negative SLE</td>
</tr>
<tr>
<td></td>
<td>Anti-La/SSB</td>
<td>+ in 25–40% Sjögren syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Both anti-Ro &amp; anti-La associated with extraglandular manifestations &amp; glandular lymphocytic infiltration)</td>
</tr>
<tr>
<td>La/SSB (present in nucleus &amp; cytoplasm)</td>
<td>Anti-Ro/SSA (Anti-Ro60 &amp; anti-Ro52)</td>
<td>+ in Sjögren syndrome 40–95% and in ANA negative SLE</td>
</tr>
<tr>
<td></td>
<td>Anti-La/SSB</td>
<td>+ in 25–40% Sjögren syndrome</td>
</tr>
<tr>
<td>Ribonucleoprotein (RNP)—RNA + Proteins</td>
<td>Anti-U1 RNP</td>
<td>MCTD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40–60% SLE (not specific)</td>
</tr>
<tr>
<td>Topoisomerase-I (Scl70)</td>
<td>Anti-Topoisomerase-I/ Anti-Scl70</td>
<td>+ in 30% cases of diffuse Cutaneous SSc, may be associated with ILD</td>
</tr>
<tr>
<td>Centromere</td>
<td>Anti-centromere Ab</td>
<td>Limited cutaneous SSc</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Cytoplasmic</td>
<td>Anti Histidyl tRNA synthetase (Anti-Jo1)</td>
<td>Polymyositis/Dermatomyositis, Strongly associated with ILD</td>
</tr>
<tr>
<td></td>
<td>Anti Ku Ab</td>
<td>With overlap syndromes, e.g., myositis + SSc or SLE, UCTD</td>
</tr>
<tr>
<td></td>
<td>Anti-mitochondrial Ab</td>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Anti-smooth muscle cell Ab</td>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>RNA Polymerase III</td>
<td>Anti RNA Polymerase III</td>
<td>DcSSc with renal involvement</td>
</tr>
<tr>
<td>PM-Scl</td>
<td>Anti PM-Scl</td>
<td>Systemic sclerosis</td>
</tr>
</tbody>
</table>

*Extraglandular manifestations – Purpura, vasculitis, lymphadenopathy, leukopenia & thrombocytopenia. DcSSc, diffuse cutaneous systemic sclerosis; ILD, interstitial lung disease; UCTD, undifferentiated connective tissue disease

Figs. 2A and B: Antineutrophilic cytoplasmic antibody (ANCA), c-ANCA, and pANCA. IIF Staining—c-ANCA, p-ANCA
Source: Dr Anuj Sharma, Consultant Pathologist, Aanvik Diagnostics, Jaipur
Kaolin clotting time 
apTT and dRVVT may sometimes be normal if there is 
a large thrombus and it may be falsely prolonged if 
the patient is on anticoagulants.

2. Anticardiolipin Ab—
   IgG, IgM, & IgA* 
   Most sensitive test for APS

3. Anti-beta-2 Glycoprotein Ab—
   IgG, IgM, & IgA* 
   (*IgA isotype is included in the SLICC criteria of SLE but these are not 
   routinely available in laboratories)

Significant APLA titers:

1. aCL IgG antibody more than 40 IgG phospholipid 
   (GPL) units or aCL IgM more than 40 IgM phospholipid 
   (MPL) units, or more than 99th percentile (measured 
   by ELISA) are significant.\(^8\) Titters are low (<40 GPL or 
   MPL), moderate (40–80 GPL or MPL) or high (>80 GPL 
   or MPL).\(^9\)

2. Anti-beta-2 glycoprotein 1 antibody of IgG and/or IgM 
   isotype in serum or plasma in titer more than 99th 
   percentile (measured by ELISA).\(^8\) 
   These tests are usually done at the time of acute 
thrombotic event and must be repeated after 12 weeks 
to exclude false positive tests secondary to infections or 
drugs (Table 5).

Complement C3 and C4

These are measured by nephelometric immunoassay. 
Normal C3 levels range from approximately 80–160 mg/
DL. Normal C4 levels range from 16–48 mg/dL.

Decreased C3 or low C3, C4 may be seen in immune 
complex-mediated diseases, viz. SLE, APS, Sjögren’s 
syndrome, MCTD, hypocomplementemic urticarial 
vasculitis, mixed cryoglobulinemia, serum sickness, 
some glomerulonephritides including post-streptococcal 
nephritis. With the treatment of these diseases, C3 or 
C4 may normalize. Low C4 with normal C3 may be seen 
in hereditary angioedema and acquired C1 inhibitor 
deficiency.

HLA B27

This test is done by flow cytometry and polymerase chain 
reaction (PCR). PCR is preferred as it gives accurate results. 
This test should be ordered when there are clinical features of 
spondyloarthritis (SpA), viz. inflammatory backache, as 
in general population 8% population is positive for HLA 
B27, so if ordered injudiciously a person with mechanical 
backache may be wrongly diagnosed as a patient of SpA. 
Ankylosing spondylitis, a subtype of SpA, 85–95% are 
positive for this gene remaining 5–15% may be negative, 
while in SpA secondary to psoriasis or inflammatory bowel 
disease and in reactive arthritis, up to 50% may be positive 
for HLA B27.\(^{10}\) False positive and false negative do occur so 
judicious ordering for this test is the need.

Serum Uric Acid (SUA)

It is lower in females (≤6 mg%) than males (≤7 mg%). SUA 
is usually assessed in the diagnosis of gout but during 
aacute gout flare, the levels may be normal or low in up 
to 40% because of release of cytokines and ACTH during 
flare, which can lower the uric acid levels. High uric levels 
leak support to the clinically suspected case of gout but 
its estimation is neither diagnostic nor mandatory for 
confirmation of the diagnosis of gout.

<table>
<thead>
<tr>
<th>TABLE 5</th>
<th>APLA positivity in diseases other than primary APS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARD*13</td>
<td>Infections (usually IgM aCL positive)</td>
</tr>
<tr>
<td>• SLE—25–50%</td>
<td>• Syphilis</td>
</tr>
<tr>
<td>• Sjögren syndrome—42%</td>
<td>• Hepatitis C infection</td>
</tr>
<tr>
<td>• Rheumatoid arthritis—33%</td>
<td>• HIV infection</td>
</tr>
<tr>
<td>• Autoimmune thrombocytopenic purpura—30%</td>
<td>• Human T-cell lymphotropic virus type 1 infection</td>
</tr>
<tr>
<td>• Autoimmune hemolytic anemia – (Unknown)</td>
<td>• Malaria</td>
</tr>
<tr>
<td>• Psoriatic arthritis—28%</td>
<td>• Bacterial septicemia</td>
</tr>
<tr>
<td>• Systemic sclerosis—25%</td>
<td>• Leptospirosis</td>
</tr>
<tr>
<td>• Mixed connective-tissue disease—22%</td>
<td></td>
</tr>
<tr>
<td>• Polymyalgia rheumatica or giant cell arteritis—20%</td>
<td></td>
</tr>
<tr>
<td>• Behçet syndrome—20%</td>
<td></td>
</tr>
</tbody>
</table>

Done by ELISA,
not affected by 
thrombosis or oral 
anticoagulants
Synovial Fluid (SF)

In monoarticular involvement, SF may be examined for bacteria (tubercle bacilli or non-tubercle bacilli), fungus, and crystals. In the suspected case of gout, SF should be aspirated may be seen under light microscope (Fig. 3) as polarizing microscope, which is ideal for the demonstration of urate crystals, is not routinely available.

Conclusion

In treating ARD, it is of utmost importance that a very good history and physical examination have been done before ordering investigations. False positives and false negatives do occur so one should be cautious in interpreting these investigations. "Arthritis panel" is to be avoided and should never be ordered.

References