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REVIEW

Pharmacotherapy Options in Rheumatoid Arthritis

Pradeep Kumar and Snehashish Banik

Rheumatology Diseases Unit, Aberdeen Royal Infirmary, Aberdeen, Scotland.
Corresponding author email: pradeepkumar@nhs.net

Abstract: Drugs form the mainstay of therapy in rheumatoid arthritis (RA). Five main classes of drugs are currently used: analgesics, non-steroidal anti-inflammatories (NSAIDs), glucocorticoids, nonbiologic and biologic disease-modifying antirheumatic drugs. Current clinical practice guidelines recommend that clinicians start biologic agents if patients have suboptimal response or intolerant to one or two traditional disease modifying agents (DMARDs). Methotrexate, sulfasalazine, leflunomide and hydroxychloroquine are the commonly used DMARDs. Currently, anti-TNF is the commonly used first line biologic worldwide followed by abatacept and it is usually combined with MTX. There is some evidence that tocilizumab is the most effective biologic as a monotherapy agent. Rituximab is generally not used as a first line biologic therapy due to safety issues but still as effective as anti-TNF. The long term data for the newer oral small molecule biologics such as tofacitinib is not available and hence used only as a last resort.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease with significant morbidity and mortality rates if left untreated.[1,2] Drugs form the mainstay of therapy in RA and current aggressive treatment strategies have greatly improved outcomes for patients with RA over the past decade. Five main classes of drugs are currently used: analgesics, non-steroidal anti-inflammatories (NSAIDs), glucocorticoids, as well as biologic and non-biologic disease-modifying antirheumatic drugs (DMARDs). Combinations of these therapies are frequently used. It is now possible to target specific elements in the immune system (eg, cytokines, B-cells, molecules that cause interaction between antigen presenting cells (APCs), and T cells) which play a key role in pathogenesis of RA. In this article we have given an update of different aspects of the pharmacotherapeutic interventions in RA.

Analgesics and NSAIDs

In RA treatment, analgesics and NSAIDs are used mainly on a temporary basis until the DMARDs take effect, as well as during disease flares. Though any analgesic can be used, acetaminophen (paracetamol) is the most commonly used analgesic due to its minimal side effects. There are at least 20 different NSAIDs which have been used and common short acting NSAIDs include ibuprofen, diclofenac, ketoprofen, and indomethacin. Naproxen, celecoxib, meloxicam, nabumetone, and piroxicam are examples of long acting NSAIDs.

The primary effect of NSAIDs is to inhibit cyclooxygenase (COX) 1 and 2, thereby impairing the ultimate transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. Several selective COX 2 inhibitors have been withdrawn from the market due to cardiovascular safety concerns, but several (celecoxib and etoricoxib) are still available for use. The lowest NSAID dose compatible with symptom relief should be prescribed and the dose should be reduced and withdrawn when a good response to DMARD treatment is achieved. Common adverse effects of these drugs include dyspepsia, peptic ulcer disease, and bleeding. It is not unusual to see transient elevations of liver enzymes with NSAIDs. Additionally, tinnitus can occur with any NSAID treatment. Both selective and non-selective COX inhibitors increase the risk of cardiovascular problems.[3] They may interfere with the beneficial antiplatelet activity of aspirin, increase blood pressure, increase risk of adverse cardiovascular events such as myocardial infarction, and can exacerbate heart failure. Other less common side effects include renal impairment, electrolyte and fluid abnormalities, bronchospasm, and aseptic meningitis. There is an overall increased risk of death in patients with pre-existing cardiovascular diseases and NSAID usage.[4]

Glucocorticoids

Glucocorticoids are frequently include in the RA treatment regimen for a short period in order to minimize disease activity in patients with active RA while awaiting a clinical response to the given DMARD being applied. Treatment with combinations of DMARDs plus glucocorticoids provides greater benefit clinically[5] and results in less radiographic progression[6] in comparison with DMARD monotherapy. As such, the disease modifying property of glucocorticoids can extend up to 24 months. However, in clinical practice it is usually withdrawn gradually after approximately 3–6 months due to its long term side effects.

Oral glucocorticoids (prednisolone), used as a short course, or parenteral long acting glucocorticoids, such as methyl prednisolone 80–120 mg or triamcinolone 80 mg, can be given intramuscularly and when required for disease flares. In general, the cumulative dose of glucocorticoids must be kept to a minimum to avoid long term side effects. The average duration of effects of intramuscular long acting glucocorticoids is about 6 to 8 weeks. Patients can experience facial flushing during the initial few days following intramuscular or intraarticular injection. Very few patients may have localized fat atrophy at the site of injection. This is usually seen in young women and reported more with triamcinolone. Skin indentation and pigmentation can also be seen over the injection site. Chronic use of low dose glucocorticoids in RA can also cause multiple adverse events including an increased risk for osteoporosis and skeletal fractures, gastrointestinal bleeding, peptic ulcer disease, diabetes mellitus, infections, cataracts, and impaired hypothalamic-pituitary-adrenal axis response. Significant cardiovascular adverse events and infections may occur. Although rare, risks associated with intraarticular injection include tendon rupture, osteonecrosis, acute synovitis (transient

post-infection flare, usually resolving within 48 hours), septic arthritis, and systemic effects.[7]

Nonbiologic DMARDS

Methotrexate (MTX), sulfasalazine (SSZ), leflunomide, and hydroxychloroquine (HCQ) are the commonly used DMARDs used in the treatment of RA. Non-biologic DMARDs require regular monitoring and a useful quick reference guide has been produced by the British Society for Rheumatology (Table 1). Monitoring parameters and frequency may have global variations. Older DMARDs such as gold, penicillamine, cyclosporine, and azathioprine have an adverse risk benefit ratio in RA patients and will be beyond the needs of modern management of RA. Other antibiotic DMARDs, such as doxycycline or minocycline, are also not used due to the availability of more effective drugs.

Methotrexate

MTX is a widely used first-line DMARD which can be used alone or in combination. It takes 6–8 weeks for the onset of its benefit. MTX can be given orally, intramuscularly, or subcutaneously. The usual starting dose is 7.5–10 mg per week and the dose is titrated up to 20–25 mg per week on a fortnightly basis. The bioavailability of oral MTX decreases with higher doses threfore subcutaneous MTX is used in patients with inadequate response despite dose escalation. MTX primarily is cleared via the kidneys with most being unchanged in the urine. Therefore, any fall in glomerular filtration rate results in sustained serum levels of the drug that may induce bone marrow or other toxicities.

MTX is a folic acid antagonist drug. By binding to dihydrofolate reductase, MTX interferes with DNA synthesis and cell replication. For the dose used in RA, its main effect is believed to be due to the inhibition of enzymes involved in purine synthesis leading to the accumulation of adenosine and thus inhibiting the T cell activation. About 60% of patients may experience mild toxicity, but more than 70% continue treatment with it at the end of the first year making it superior to other non-biologic DMARDs.

Common adverse effects include nausea the day after the dose is taken, mouth ulcers, reversible alopecia, rash, and increased rheumatoid nodule formation. Rarer adverse effects include bone marrow suppression, liver cirrhosis (increased with alcohol consumption), and pulmonary infiltrates/allergic pneumonitis. Folic acid at the dose of 5–10 mg per week is always given 2–3 days after MTX. Taking folic acid 6 days a week reduces gastrointestinal and mucosal adverse effects and is recommended for people who develop these side effects. Blood tests monitoring must be done in patients who are taking MTX. Full blood count, liver function tests, and creatinine must be checked. The frequency of blood tests monitoring varies according to the national guidelines. The role of monitoring pulmonary function in patients taking MTX is not known, but it is usually not done in current practice due to the cost and resources involved. A baseline chest x-ray is generally performed. MTX should not be used in patients with pre-existing bone marrow aplasia or cytopenias, immunodeficiency, severe hepatic disorders, or active infectious disease. Concomitant alcohol intake or hepatotoxic drugs are also contraindicated, however in clinical practice alcohol within the recommended limits for cardiovascular benefits are allowed. MTX is clearly contraindicated in pregnancy and in the women of child bearing age due to the risk of teratogenicity. Trimethoprim or trimethoprim-sulfamethoxazole can increase bone marrow suppression, probably by an additive antifolate effect, and is usually avoided. Hepatotoxicity is potentially increased with the co-administration of

Table 1. Quick reference guideline for monitoring of DMARD therapy, British Society for Rheumatology (November 2009).

Nonbiologic DMARD	Monitoring parameters
MTX	Complete blood count (CBC) fortnightly until 6 weeks after last dose increase; if this remains stable, monthly. Thereafter monitoring may be reduced in frequency, based on clinical judgement. Liver function tests (LFTs): 3 monthly Renal Function test: 6–12 monthly
SSZ	CBC and LFTs monthly for 3 months and 3 monthly thereafter
HCQ	Annual review by an optometrist
Leflunomide	CBC, LFTs every 6 months and if stable 2 monthly thereafter

azathioprine, SSZ, or leflunomide as part of combination therapy.

Sulfasalazine

SSZ contains an anti-inflammatory and an antibacterial agent (5-aminosalicylic acid and sulfapyridine). 6–12 weeks are required for the onset of its action. Tablets should be administered in evenly divided doses, preferably after meals at the recommended dosage range of 30–50 mg/kg/day. In clinical practice, SSZ dose is started at 500 mg/day and is increased by 500 mg weekly to 2.0–3.0 g/day.

SSZ operates by impairing folate absorption. Only 15% of the drug is absorbed as unchanged drug from small intestine. SSZ is cleaved in the colon by bacterial enzymes to release acetylsalicylic acid and sulfapyridine. SSZ is excreted primarily by urine (as unchanged drug, conjugates, and acetylated metabolites) and in small amounts by feces. The mechanism of action of sulfapyridine is unclear but may involve inhibition of the transcription factors which are increased in inflammation.

The combination therapy of MTX, SSZ, and HCQ results in better clinical outcome than MTX alone, MTX plus SSZ, or MTX plus HCQ in patients with a poor response to MTX or another unaccompanied DMARD.[8] The efficacy of SSZ plus MTX is uncertain in comparison to either drug alone. A molecular rationale for the failure of combination of SSZ and MTX to be more efficacious than either drug given alone was provided in a Dutch study which found SSZ to be a potent inhibitor of the principal cell membrane transporter for folates as well as MTX, along with inducing cellular folate depletion.[9]

Up to 30% of patients taking SSZ experience mild gastrointestinal disturbances (nausea, vomiting, loss of appetite, diarrhea), skin rash, and pruritus. Neurological symptoms of headache, dizziness, or depression also occur. In males, oligospermia with impaired motility are also observed. This, however, does not act as a contraceptive and reverses three months after treatment is stopped. Rarer adverse effects include leucopenia, bone marrow depression, hemolytic anemia in patients with glucose-6-phosphatedehydrogenase deficiency, abnormal liver function tests, hepatitis, and abdominal pain. As SSZ inhibits absorption of folate, it can cause folate deficiency. Full blood count and liver function must be checked. The frequency of blood tests monitoring is less than what is needed for MTX and varies according to the national guidelines. SSZ should not be prescribed for patients who are hypersensitive to salicylates or sulfonamide derivatives. It is also contraindicated in patients with hematological, renal, or hepatic dysfunction. SSZ is safe to be used during pregnancy.

Hydroxychloroquine

HCQ is primarily used in combination with other DMARDs. In patients with mildly active RA, particularly those without poor prognostic features or with findings limited to mild inflammatory arthritis and a positive antinuclear antibody test (in whom a distinction cannot be made between early RA and early systemic lupus erythematosus), HCQ is usually used rather than SSZ or MTX as the initial DMARD. It has a slow action onset of 2–6 months. The drug is metabolized in the liver and metabolites include desethylhydroxychloroquine and desethylchloroquine. HCQ is excreted by urine as metabolites and up to 60% as unchanged drug. HCQ functions by interfering with antigen presentation and the activation of the immune response by increasing pH within macrophage phagolysosomes. Common side effects include epigastric burning, nausea, bloating, diarrhoea, skin rashes, and alopecia. HCQ may also exacerbate psoriasis and patients may develop hyper pigmentation in sun exposed areas. Retinal toxicity with macular damage is infrequent, however it is recommended that patients wear sunglasses in strong sunlight. Corneal deposits (reversible if the drug is ceased) are seen in less than 0.1% of patients. However, the risk increases if the dose exceeds 6 mg/kg/day. The usual starting dose in adults is 400 mg/day which can be decreased to 300 mg/day after 3 months. Ophthalmological monitoring is a controversial area as it was originally developed for chloroquine with its greater ocular toxicity. Baseline ophthalmological review is recommended for patients with pre-existing eye disease or diabetes and then every 6 months thereafter. Patients with pre-existing maculopathy should not take HCQ. No specific laboratory monitoring is required. HCQ is considered to be safe for use during pregnancy.

Leflunomide

Leflunomide is the newest of the commonly used DMARDs given with the loading dose of 100 mg/day

for three days followed by 10–20 mg/day.[10] In order to minimize the initial side effects, it is not uncommon to reduce or not give the loading dose particularly in elderly or patients with other co-morbid illnesses. Leflunomide is a prodrug in which the active metabolite is responsible for its activity. Its metabolism is hepatic to an active metabolite M1 (also known as teriflunomide), which accounts for nearly all pharmacologic activity. Further metabolism proceeds to multiple inactive metabolites which undergoes enterohepatic recirculation. Enterohepatic recycling appears to contribute to the long half-life of this agent, as activated charcoal and cholestyramine substantially reduce plasma half-life. The drug is excreted both in feces and urine.

Leflunomide is an immune-modulatory agent which primarily inhibits replication of activated lymphocytes by blocking the de novo synthesis of pyrimidines and, therefore, DNA. It also has a weak anti-inflammatory action. The most common adverse effects are nausea and diarrhoea which are experienced by 20%–30% of patients, but these may settle with continued treatment. Skin rash and reversible alopecia occur in 5%–10% of patients and elevations of liver enzymes (AST and ALT) occur with sole use of leflunomide, and affect up to 60% of patients if used in combination with MTX.[11] Rarer adverse effects include severe bone marrow suppression, infections, and persistent abnormal liver function tests despite dose reduction. New onset hypertension has been reported in patients starting on leflunomide. Blood pressure must be measured before the start of treatment and periodically thereafter. Full blood count, creatinine, and liver function should also be monitored periodically as per the national guidelines. Leflunomide should not be given to patients with severe immunodeficiency, impaired bone marrow function, or severe uncontrolled infections. As liver impairment is also a complication, excessive alcohol consumption should be avoided. As leflunomide inhibits cytochrome P450 2C9, it can interfere with drugs such as phenytoin and warfarin.

Biologic DMARDs

Biologic therapies include the tumor necrosis factor (TNF) alpha inhibitors, anti-B cell therapy, T-cell co-stimulation blocker, anti-Interleukin 6 (IL-6), anti-Interleukin 1 (IL-1), and protein kinase inhibitors. Apart from efficacy and side effects, dosing, route of administration, cost and national guidelines would also influence choosing a drug for a patient. There is a standardized nomenclature for these biologic agents: if the name ends with "cept" it is a receptor; if it ends with "mab," "zumab," "mumab," or "inib" it suggests chimeric monoclonal antibody, humanized monoclonal antibody, fully human monoclonal antibody, or small molecule kinase inhibitors, respectively.

Anti-TNF

TNF is a cytokine involved in systemic inflammation which is abundant in the serum and synovial fluid of patients with RA and it plays a major role in the pathogenesis of RA. Infliximab, etanercept, adalimumab, certolizumab, and golimumab are currently available anti-TNF agents and their introduction has marked the start of a revolution in the field of RA. They are very effective with 60%, 40%, and 20% of ACR 20, 50, and 70 responses, respectively. Its long term effects, however, are not known. Some patients can also develop antibodies against these agents which can decrease its efficacy. These autoantibodies are seen more commonly in monoclonal antibodies than a receptor.

Anti-TNFs share common side effects which include headache, abdominal pain, diarrhoea, vomiting, rash, injection site reaction, bleeding, bruising, itching, respiratory tract infection, and other infection such as cellulits (*Listeria* being the most likely organism), positive anti-double-stranded DNA antibodies, positive ANA (11%), and reactivation of latent tuberculosis (TB). This risk of reactivation of *Mycobacterium tuberculosis* infection is greater with infliximab and adalimumab than with etanercept. The chance of non-tuberculous mycobacterial infections are also higher with anti-TNFs. Cases of TB occurring in association with TNF-alpha inhibitors have a higher likelihood of involving extrapulmonary sites and of being disseminated at presentation when compared with other TB cases. Appropriate TB screening is recommended based on the local guidelines. In patients from high endemic regions, chest X-ray, Heaf/Mantoux test, and quantiferron gold/T-spot assay must be performed as part of screening for latent TB. Patients with latent TB must be treated first for at least one month prior to starting anti-TNF therapy.

The risk of developing malignancy in patients treated with anti-TNF therapy is slightly controversial. Bongartz et al's[12] meta-analysis suggests increased rate of malignancy with the pooled odds ratio (OR) of 3.3 (95% confidence interval (CI), 1.2–9.1) Many malignancies were non-melanoma skin cancer (NMSC). On the contrary, analysis of a Swedish registry by Simard et al[13] did not find any increase in the overall cancer risk (standardized incidence ratio of 1.1; 95% CI, 0.6–1.8) in patients receiving anti-TNF therapy compared with those which were not. The most recent data from a large U.S. observational study concluded that biologics use in RA treatment was not associated with increased overall risk of any malignancy. However, when examined separately, the risks for both NMSC and melanoma were increased with biologic therapy (OR: 1.5; 95% CI, 1.2–1.8; OR: 2.3; 95% CI, 0.9–5.4, respectively). Pulmonary fibrosis was increasingly reported in several national registry data and in post-marketing surveillance.

Anti-TNF is contraindicated in patients with the history of demyelination, active infection such as leg ulcers or long term urinary catheter, and in patients with heart failure NYHA grade 3 or 4. It is also not currently recommended in women who are pregnant or breast feeding, though it is increasingly being used in pregnancy and thus far has been found to be safe. Caution should be exercised in the use of anti-TNFs in patients with previous malignancy. If patients have been free of any recurrence of their malignancy for 10 years, there is no evidence for a contraindication to anti-TNF therapy. All anti-TNFs (infliximab, etanercept, adalimumab, certolizumab, and golimumab) have been found to be more effective when used in combination with MTX.[14–20] The route of administration, dose, and frequency of the available anti-TNF therapies are shown in Table 2.

Anti-B-cell therapy

B cells play an important role in the pathogenesis of RA. These cells are targeted by using antibodies against the pan-B-cell surface marker CD-20. Other targets such as anti-CD 19 are still under evaluation. Rituximab is currently the only licensed anti-B cell therapy in RA.

Rituximab

Rituximab is a monoclonal antibody directed against the CD20 antigen on B-lymphocytes. CD20 regulates cell cycle initiation and, possibly, functions as a calcium channel. Rituximab binds to the antigen on the cell surface, activating complement-dependent B-cell cytotoxicity, as well as to human Fc receptors, mediating cell killing through an antibody-dependent cellular toxicity.

As an intravenous infusion, 1 g is prescribed on days 1 and 15 in combination with MTX; subsequent courses may be administered every 24–52 weeks (based on clinical evaluation), and if necessary may be repeated earlier, but no sooner than every 16 week. B-cell recovery begins about 6 months following completion of treatment and median B-cell levels will return to normal by 12 months following completion of treatment. B lymphocyte depletion treatment using a combination of rituximab plus MTX has been effective in randomized trials of patients resistant to MTX alone as well as those resistant to TNF inhibitors.[21,22] Preliminary data from long term safety follow up studies suggest a similar safety profile to other biologics. However, concerns regarding rare reports of progressive multifocal leukoencephalopathy with rituximab[23] have resulted in use of this combination primarily in patients in whom TNF inhibitors have been inadequate. Furthermore, rituximab was found to be more effective in patients who are seropositive for rheumatoid factor or anti-CCP antibodies.

Table 2. Route of administration, doses and frequency of anti-TNFs.

Anti-TNF	Route of administration	Dose and frequency
Etanercept	Subcutaneous	Either as 25 mg twice a week or 50 mg once a week.
Adalimumab	Subcutaneous	40 mg every other week. Patients not taking MTX may increase dose to 40 mg every week.
Infliximab	Intravenous	3 mg/kg dose at 0, 2, and 6 weeks, followed by 3 mg/kg every 8 weeks thereafter.
Certolizumab pegol	Subcutaneous	Initial loading dose of 400 mg, repeated with the same dose at 2 and 4 weeks. Maintenance dose is 200 mg every other week
Golimumab	Subcutaneous	50 to 100 mg per month.

Patients treated for RA with rituximab may experience infusion related reactions. To prevent it, premedication with 100 mg of intravenous methylprednisolone and an antihistamine is always given.

T-lymphocyte co-stimulation blocker

T-cells require two signals in order to be fully activated. The first signal is between the T-cell receptor and major histocompatibility complex (MHC) on the APCs. The second co-stimulatory signal is between CD28 on T-cells and CD80/CD86 on the APCs. Another co-stimulatory receptor (inducible co-stimulator) in T-cells has also been described but has not yet been explored as a therapeutic target.

Abatacept

Abatacept is a selective co-stimulation modulator which inhibits T-cell (T-lymphocyte) activation by binding to CD80 and CD86 on APC and thus blocking the required CD28 interaction between APCs and T-cells. Abatacept can be administered either intravenous or subcutaneously. Intravenous dosage is dependent on the body weight. 500 mg is given for patients who are less than 60 kg, 750 mg for those who are 60–100 kg, and 1000 mg if the patients are over 100 kg. This dose is repeated 2 and 4 weeks after initial infusion, then every following 4 weeks. Subcutaneously, 125 mg is given on a weekly basis. It is effective in patients with active RA and failed on at least one DMARD. It has also been effective in patients who have not adequately responded to the combination of MTX with a tumor necrosis factor inhibitor.[24] Chronic obstructive pulmonary disease (COPD) patients experience a higher frequency of COPD-related adverse reactions with Abatacept. Other side effects include headache, nausea, nasopharyngitis, infection (adults 54%; children 36%), and antibody formation (2% to 41%).

Anti-interleukin-6

IL-6 plays a key role in driving the inflammation and synovial cell proliferation that characterize RA joint destruction. Tocilizumab is the only currently available anti-IL-6.

Tocilizumab

Tocilizumab is an antagonist of the IL-6 receptor. It is given intravenously at a dose of 8 mg/kg once a month. Endogenous IL-6 is induced by inflammatory stimuli and mediates a variety of immunological responses. Inhibition of IL-6 receptors by tocilizumab leads to a reduction in cytokine and acute phase reactant production. Tocilizumab is effective when used together with MTX in patients who have had an inadequate response to MTX alone or to MTX and anti-TNF. Raised liver enzymes and cholesterol are seen with tocilizumab therapy. Increased infection rates are expected. In ADACTA trial[25] tocilizumab was superior to monotherapy with adalimumab in reducing signs and symptoms of RA in MTX intolerant patients or patients for whom MTX treatment was considered ineffective or inappropriate.

Anti-interleukin-1

IL-1 is another important pro-inflammatory cytokine in the pathogenesis of RA. Plasma and synovial fluid concentration of IL-1 are elevated and correlate with rheumatoid disease activity. Anakinra is the only anti IL-1 drug tried in RA treatment.

Anakinra

Anakinra is an antagonist of the IL-1 receptor. Endogenous IL-1 is induced by inflammatory stimuli and mediates a variety of immunological responses, including degradation of cartilage (loss of proteoglycans), and stimulation of bone resorption. Anakinra is given subcutaneously at the dose of 100 mg daily. The combination of anakinra when added to a stable dose of MTX was effective in patients with moderate to severe RA in a 24-week trial.[26] Although additional studies have also shown benefit, anakinra is now rarely used in RA as it is significantly less potent than TNF inhibitors in most patients.

Protein kinase inhibitors

The protein kinases are small intracellular molecular enzymes which modify the function of other proteins by attaching phosphate groups to them. Over 160 kinases have been described. Most kinases act on serine, threonine, or tyrosine. Janus kinase (JAK) is a tyrosine kinase and four of its kinds have been described: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2).

JAK inhibitors

Kinase inhibitors selectively inhibit JAKs which mediate signaling of cytokine and growth factors

responsible for hematopoiesis and immune function. JAK mediated signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors which leads to modulation of gene expression. These small molecules can be taken orally, making this treatment unique. Tofacitinib is a JAK inhibitor recently approved by the FDA at the dose of 5 mg twice daily in patients with moderately to severely active RA who have had an inadequate response or intolerance to MTX.[27] It can be used as a monotherapy or in combination with MTX or other non-biologic DMARDs but should not be used in combination with biologic DMARDs. Patients treated with tofacitinib are at increased risk for tuberculosis and serious infections, which may lead to death. Most patients who developed these infections were taking other immunosuppressants alongside. Lymphoma and other malignancies have been observed in patients treated with tofacitinib. Elevated cholesterol has also been noted with this drug usage. Long term safety issues are not yet known.

Conclusion

The last two decades have seen a great revolution in the management of RA due mainly to increased pharmacotherapeutic options. Both biologic and non-biologic DMARDs have significantly improved the outcome in patients with RA and must be initiated as early as possible. Current clinical practice guidelines recommend that clinicians start biologic DMARDs if patients have suboptimal response or intolerant to one or two non-biologic DMARDs. There is still no firm evidence that early initiation of a biologic regimen can improve the long-term prognosis of RA and more studies are needed to justify its usage as a first-line DMARD. MTX, SSZ, leflunomide, and HCQ are the commonly used DMARDs. There is still no consensus as to which biologics should be used and in what order as it depends on several factors including cost and route of administration. Currently, anti-TNF is the commonly used first line biologic worldwide, followed by abatacept, and it is usually combined with MTX. There is some evidence that tocilizumab is the most effective biologic as a monotherapy agent. Rituximab is generally not used as a first line biologic therapy due to safety issues, but is still as effective as anti-TNF. Monoclonal antibodies seem to produce more immunogenicity than other types of biologics. The long term data for the newer small oral molecule biologics such as tofacitinib, is not yet available and hence should be used only as a last resort.

Author Contributions

Reviewed the literature: SB. Wrote the first draft of the manuscript: SB. Made critical revisions and contributed to the writing of the manuscript: PK. Jointly developed the structure and arguments for the paper: PK, SB. Both authors reviewed and approved the final manuscript.

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