INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Glucocorticoid-Sparing Strategies in Rheumatoid Arthritis: Current Approaches and Emerging Therapies

Fathima Nazar*, Sajitha G

Department of Pharmacy Practice, College of Pharmaceutical Sciences, Govt Medical College TVM, Kerala, India

ARTICLE INFO

Published: 29 Jun 2026
Keywords:
Adverse effects, Bridging therapy, csDMARDs, Disease, Glucocorticoid, Rheumatoid arthritis, Tapering, tsDMARDs.
DOI:
10.5281/zenodo.21053525

ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by progressive joint destruction, disability, and premature death. Glucocorticoids play an important role in reducing disease progression and achieving clinical remission. However, long-term steroid use is associated with complications such as osteoporosis, diabetes mellitus, cardiovascular effects, and adrenal suppression. Therefore, glucocorticoid tapering is essential to minimize treatment-related complications. The European Alliance of Associations for Rheumatology (EULAR) guidelines recommend using glucocorticoids at the lowest effective dose for the shortest possible duration. Prednisone doses greater than10 mg/day are associated with an increased risk of adverse events. The success of glucocorticoid tapering may be influenced by several factors, including age, comorbidities, disease duration, patient characteristics, and treatment efficacy. Among the available treatment options for rheumatoid arthritis, tofacitinib has demonstrated better steroid sparing effects compared with other DMARDs including conventional synthetic DMARDs (csDMARDs) and biologic DMARDs bDMARDs). This review focuses on current glucocorticoid sparing strategies including gradual tapering methods, monitoring of disease flare and assessment using DAS28. A multidisciplinary approach involving rheumatologists, pharmacists, physiotherapists, and patient education play a crucial role in improving adherence, monitoring disease activity, and optimizing tapering outcomes. Emerging therapeutic approaches such as personalized medicine and biomarker-guided treatment may further enhance glucocorticoid-sparing strategies and improve long-term patient outcomes in rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis is a chronic systemic autoimmune inflammatory disease characterized

***Corresponding Author:** Fathima Nazar
Address: *College of Pharmaceutical Sciences, Govt Medical College TVM, Kerala, India*
Email : Fathimanazar1033@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

by progressive destruction of joints, disability and premature death. The incidence is more in people older than 40 years. The exact pathogenesis is unknown but it involves interaction of genetic and environmental risk factors. Genetic predisposition, especially variations associated with HLA genes increases the susceptibility, while environmental triggers such as smoking, obesity, infection and alteration in gut microbiome may initiate or worsen the autoimmune process [1]. In RA, immune-mediated inflammation leads to synovial membrane thickening and infiltration of inflammatory cells into the joints. This inflammatory response promotes the release of pro-inflammatory cytokines, autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) contribute to disease progression and joint damage [2].

Clinical manifestations involve gradual onset of pain and swelling. Early morning stiffness lasts for 30 min or several hours and is often accompanied by fever, fatigue and weakness. Extra articular manifestations include nodules, lymphadenopathy, vasculitis, scleritis etc. The global disease burden for RA is crucial. The Global Burden of Disease Study (GBD) 2021 is important tool for investigating the burden of disease. According to the study findings from 1990 to 2021, the number of individuals living with RA increased worldwide [3,4]. In 2021, ~ 17.9 million were affected globally, representing a substantial rise compared to 1990 [5].

Increasing life expectancy, aging population, environmental risk factors and smoking have been identified as important contributions to the growing burden of RA globally [6]. In addition, DALYs associated with RA remained significant, demonstrating the considerable impact of the disease on physical function, quality of life and health care system worldwide [7]

Glucocorticoids affect the inflammatory cascade of RA by inhibiting fibroblast, macrophages and pro-inflammatory cytokines such as IL-1, IL-6 and TNF-alpha. Their use within the first 2 years of disease progression may reduce the structural damage [8]. Low dose glucocorticoids are commonly used in chronic RA and are recommended mainly as “bridging therapy” [9]. However, long term use is associated with adverse effects such as weight gain, gastric ulcer, osteoporosis, cardiovascular complications and infections [10]. Therefore, glucocorticoid tapering is necessary to reduce these complications. The ACR guidelines recommend using the lowest effective steroid dose and tapering should be done carefully to avoid adrenal insufficiency, glucocorticoid withdrawal syndrome.

The introduction of conventional DMARDs, biological DMARDs and targeted synthetic DMARDs has improved disease control and enabled successful steroid tapering in many patients. Consequently, steroid sparing approaches have become an important therapeutic goal in modern rheumatoid arthritis management [11,12]. The present review focusses on current and emerging steroid sparing approaches in rheumatoid arthritis and highlights the importance of minimizing long-term glucocorticoid use while maintaining effective disease control.

ROLE OF GLUCOCORTICOID IN RHEUMATOID ARTHRITIS

MECHANISM OF ACTION

The main endogenous glucocorticoid in humans is cortisol, synthesised from cholesterol by the adrenal cortex. Synthetic steroids are widely used in rheumatology to treat systemic inflammation [13]. Their action occurs through binding to glucocorticoid receptors, followed by receptor activation and translocation into the nucleus where

gene expression is modified. Glucocorticoids suppress the activity of immune cells such as T-lymphocytes and macrophages, thereby reducing synovial inflammation, pain and joint damage in rheumatoid arthritis [14].

THERAPEUTIC ROLE IN RHEUMATOID ARTHRITIS

Glucocorticoids are used in rheumatoid arthritis to reduce disease activity and helps to achieve clinical remission. They provide rapid symptomatic relief and are commonly prescribed as short-term therapy during the initial stages of treatment. They may also be used as bridging therapy when initiating or changing csDMARD treatment. Current recommendations suggest gradual tapering within the 3 months exceptionally by 6 months [15].

BRIDGING THERAPY

Bridging therapy refers to the short-term use of glucocorticoids during the initiation of DMARDs until slower-acting DMARDs achieve their therapeutic effects. Conventional synthetic DMARDs, such as methotrexate, may require several weeks to months to produce clinical improvement. The COBRA trial demonstrated that combination therapy with prednisolone, methotrexate and sulfasalazine resulted in better clinical outcomes than DMARD therapy alone. This approach aims to maximize early disease control while minimizing long-term glucocorticoid exposure and steroid-related complications [15,16].

2. ADVERSE EFFECTS OF LONG-TERM STEROID THERAPY

Long term glucocorticoid therapy is associated with several adverse effects including skeletal, metabolic, endocrine, cardiovascular and immune systems. The risk increases with higher doses and prolonged duration of therapy

Osteoporosis:

Glucocorticoid- induced osteoporosis is one of the most common adverse effects in patients receiving long-term high oral dose of glucocorticoid therapy. Individuals treated with systemic glucocorticoids had lower bone mineral density (BMD) and higher morbidity of fractures as compared with healthy individuals and treated with non-glucocorticoid [17]. Excess glucocorticoid exposure may disrupt bone homeostasis by impairing bone formation and increasing bone resorption, making it a major cause of secondary osteoporosis.

Glucocorticoid induced osteoporosis results from two phases: initial rapid phase (6-12% loss) followed by a slower long-term phase with slower rate of bone loss with 3% per year. The rate of fracture is influenced by the duration of use (cumulative dose) and the current dose. Glucocorticoids promote apoptosis of osteoblast and osteocytes while inhibiting osteo blastogenesis, resulting in reduction of BMD [18,19].

Diabetes mellitus and hyperglycaemia:

Glucocorticoid induced hyperglycaemia is one of the significant metabolic complications arise from the use of glucocorticoids. It occurs due to impaired glucose tolerance and decreased insulin sensitivity. It commonly develops during the 2^{nd} to 4^{th} week of glucocorticoid therapy and it is characterized by elevated postprandial and evening glucose levels. Individuals with pre-existing diabetes mellitus should be screened when low dose glucocorticoids are prescribed for 1 month. The incidence of glucocorticoid induced hyperglycaemia is ~32% [20]. These are mediated

through the specific glucocorticoid receptor and binding with specific target genes and alter gene expressions affecting the liver, skeletal muscles, adipose tissues, pancreas, bone tissue and central nervous system. In liver, glucocorticoids promote hepatic gluconeogenesis and hepatic insulin resistance, thereby hepatic dysregulation leading to glucocorticoid induced diabetes mellitus [21]. Dose dependant effects of glucocorticoids producing hyperglycaemia due to daily oral hydrocortisone-equivalent dose starting at 20 mg/day and increasing to ≥ 120 mg/day [20].

Cardiovascular effects

It is the major cause of morbidity and mortality. Patients are at risk of increased stroke recurrence, myocardial infarction, heart failure, accelerated premature atherosclerosis, myocarditis, vasculitis and rare pericarditis. The use of ≥ 5 mg prednisolone equivalent per days doubled the risk of cardiovascular events. The cardiovascular risk is dose-dependent and was found in patients receiving medium glucocorticoid dose of 7.5 mg daily prednisolone or above for 6 months compared to those receiving <7.5 mg for 6 months. The mechanism involves the mineralocorticoid effects including increased water and sodium resorption and further activation of receptors that promote vasoconstriction [22,23].

Adrenal suppression

Adrenal suppression is an important endocrine adverse effect of prolonged glucocorticoid therapy. Hypothalamic pituitary adrenal axis (HPA) suppression is one of unwanted effects of glucocorticoid treatment and is influenced by factors like glucocorticoid dose, potency, duration of therapy, mode of administration and concomitant drugs affecting glucocorticoid metabolism. Hight risk of glucocorticoid induced adrenal suppression arise from the use of high dose GC for long term treatment. The screening tool for HPA axis suppression involve testing serum cortisol level at early morning. It should be done once glucocorticoid treatment is reduced to physiologic dosing of approximately 3-5 mg/day of prednisone. The cortisol value less than 5microgram/dl indication of adrenal insufficiency [23].

Table 1: Adverse effects and Management of Glucocorticoids [23]

Adverse Effects	Mechanism	Clinical Impact	Treatment
Osteoporosis	Increased bone resorption and impaired bone formation.	Fractures	Use low steroid dose, vitamin D and calcium supplementation for patients on glucocorticoid over 3 months.
Diabetes mellitus	Decreased insulin sensitivity and impaired glucose tolerance.	Glucocorticoid induced hyperglycemia	Monitor blood glucose level, screen for symptoms like polyuria, polydipsia and taper steroids gradually.
Hypertension	Increased sodium and water reabsorption	Elevated bp, cardiovascular complications	Bp monitoring, dose reduction, anti-hypertensive therapy.
Infection risk	Immuno-suppression	Increased susceptibility to infections	Screening the patients for any infection like Tb, HZ before taking steroids, age-appropriate vaccines should be given prior to initiating glucocorticoid therapy.
Gastrointestinal effects	Increased gastric acid secretion and reduced gastric mucosal protection	Gastric ulcer, GI bleeding, gastritis	Avoid NSAIDs along with steroids, use lowest effective steroid, take proton pump inhibitors in high-risk patients.

3. NEED FOR STEROID SPARING STRATEGIES [24,25]

- According to EULAR guidelines, GC is used as bridging therapy for rheumatoid arthritis.
- Lowest effective dose for shortest possible duration is highly recommended.
- Intake of glucocorticoids at high doses for long-term are associated with harm, it is generally recommended that GCs are tapered and stopped.
- It is essential to minimize the wide range of GC-related adverse events.
- In rheumatology, prednisone doses ≥10 mg/day are associated with an increase in adverse events.
- In the SEMIRA trial, 259 patients receiving tocilizumab and prednisone 5 mg/day with stable low disease activity were tapered by 1 mg every 4 weeks to achieve 0 mg at week 16.

Importance of monitoring during tapering [26]

- Regular monitoring of disease activity and adjustment in the medication following a fixed protocol to achieve the target treatment goal which is more beneficial than the conventional treatment.
- These approaches have been shown to reduce organ damage and complications in the conditions.
- The treat-to- target concept, revised in 2014, incorporates 4 main principles: the use of measurable indicators of disease activity (like the number of swollen and tender joints), global assessment by physician and patient and detection of inflammation through laboratory tests.

TREAT TO TARGET PRINCIPLES IN RA [27]:

- Clinical remission should be considered as the primary goal of RA management.
- Low disease activity may be alternative in some patients.
- By using validated assessment tools, disease activity should be monitored regularly.
- If the desired therapeutic target is not being achieved, treatment should be modified.
- Regular assessment is recommended in patients with active disease.
- Low disease activity or sustained remission should be maintained over time.
- The structural damage and functional status should be considered during treatment decision.
- Shared decision making between physician and patient are important in RA management.
- Early and effective therapy can help to prevent irreversible joint damage.
- Minimization of long-term glucocorticoid exposure is an important treatment objective.

EULAR RECOMMENDATION 2022 UPDATES [28]:

Treatment should begin soon after the diagnosis of RA. It should be aimed at reaching the target of low disease activity/sustained remission in every patient. Monitoring should be done every 1-3 months after the start of therapy, even if the target

is not achieved within the 3 months, therapy should be adjusted. Methotrexate should be considered as the first-line therapy. If it is contraindicated, leflunomide or sulfasalazine should be considered as first-line. After initiating or changing csDMARDs, short-term glucocorticoids in different route of administration and different dosage regimen should be considered, but should be tapered gradually when it is feasible. Due to the poor prognostic factors, the treatment target is not achieved with the first line csDMARDs therapy; switch to other csDMARDs. Biologic DMARDs and JAK inhibitors should be added, if the treatment target is not achieved with csDMARDs. Patients in sustained remission should be considered with dose reduction of DMARDs (bdmard / tsDMARD) and csDMARD even after GCs have been discontinued.

Table 2: ACR Recommendations for Treat to Target Management in RA [27]:

Disease Activity	Prognostic Features	Recommended Therapy
Low RA activity (<6 months)	Without poor prognosis	DMARD monotherapy
Moderate RA activity	Poor prognosis present	Combination DMARD therapy
High RA activity	Poor prognosis	TNF inhibitor +MTX / combination DMARD
Established RA (>6 months)	Persistent disease activity	Add / switch biologic DMARD or JAK inhibitor

4. STEROID SPARING STRATEGIES AND MONITORING

Gradual tapering methods

Glucocorticoids are the important medications to treat RA. It is generally prescribed at lowest dose for possible short duration. Increased efficacy can be found when glucocorticoid is added to the DMARDs compared with monotherapy. COBRA trial found better outcomes in combination therapy compared to monotherapy. Low dose<10 mg/ day are generally used in majority of studies. High dose 60 mg/ day must be tapered to 7.5 mg/ day in 6 or 7 weeks. If patient started with prednisone> 75 mg daily and continue for 3 months, vitamin D and calcium supplementation must be prescribed. After tapered glucocorticoids, if the patient remains in persistent remission, consider tapering bDMARDs, especially if treatment combined with conventional synthetic DMARDs [29].

Monitoring diseases flare

The major concern about the use of GC discontinuation was increased risk of disease flare compared with glucocorticoid continuation. High risk of disease flare occurs when glucocorticoid was stopped suddenly within one month of bridging therapy of 20 mg/ day hydrocortisone. The threshold doses below 5 mg/day but above 0 mg/ day were considered as flare-safe. In SEMIRA trial, most flares occurred late in the tapering procedure at 1 mg / 0 mg/ day considered as delayed effects. Glucocorticoids doses in 6 months period with DAS28CRP increase of >1.2 and current DAS28CRP>3.2 occur preceding a flare compared with GC doses in 6month period not followed by a trial [30].

DAS28 monitoring [3]

It is used to evaluate treatment response and to monitor disease activity in RA patients during GC tapering. It includes swollen joint count, tender joint count, inflammatory markers such as ESR/CRP and patient global assessment to assess disease severity.

- DAS28 score<2.6 indicates remission

- DAS28 score between 2.6 -3.2 low disease activity
- The DAS28 score helps to identify the disease flare and supports individualized tapering strategies.
- Remission target was DAS< 2.6

Challenges for tapering [30]

- Long-term safety concerns for glucocorticoid remain.
- High quality RCT are needed for glucocorticoid tapering.
- There is no required protocol to assess whether there is a safe GC doses when considering long term treatment.
- Risk of relapse or flare.
- Fear of symptoms recurrence
- Difficult to achieve sustained remission
- Long term steroid dependence
- Lack of standardized tapering protocol
- Individualized tapering

Tapering should be individualized based on patient characteristics, disease severity, duration of remission, response to DMARD therapy [31].

5. CsDMARD AS STEROID SPARING AGENTS:

csDMARDS are considered as the cornerstone in the management of RA. Commonly used csDMARDs include Methotrexate, sulfasalazine, Hydroxychloroquine and leflunomide. These agents help to control inflammation, prevent joint damage progression, reduce disease activity.

Methotrexate:

It is considered as the first-line csDMARD in the treatment of RA and is regarded as the anchor drug. The mechanism involves the inhibition of dihydrofolate reductase and promotion of adenosine release, resulting in suppression of inflammatory cytokines. Methotrexate is usually given as weekly oral/SC and can be used as monotherapy or in combination with other csDMARDs / bDMARDs. It lowers the disease activity and greater efficacy as fast as possible than other csDMARDs. Folic acid of 5 mg usually co-administered to reduce the frequency of side effects.

Leflunomide:

It is an alternative to methotrexate, when it is contraindicated. The main mechanism involves the inhibition of dihydroorotate dehydrogenase (DHODH), an enzyme involved in the pyrimidine synthesis. It is usually prescribed as a daily dose of 20 mg and is associated with hepatic and hematological toxicity. Like methotrexate, leflunomide has shown low disease activity and remission in 25% of early RA patients [3,32].

Sulfasalazine:

It has been shown to suppress inflammatory activity and joint erosion in RA patients. The mechanism of action is not fully understood. Dose up to 3 g daily may be used. Nausea is the most frequent adverse events observed [3].

Hydroxychloroquine:

It is a derivative of chloroquine and has been used in the treatment of RA. It has moderate efficacy and has been used as monotherapy. Mechanism is

not fully understood but it includes regulation of cytokine production, stabilization of lysosomes as well as protection of the cartilage [32]. It is available as a 200 mg tablet. It is preferred over chloroquine due to lower risk of retinal toxicity. It has been used safely during pregnancy [3].

Role of csDMARDs in glucocorticoid tapering:

Glucocorticoids are generally act as bridging therapy in the management of RA and helps to achieves fast remission [33]. Poor combination of tolerability arises from the combined use of methotrexate and glucocorticoids, achieving ACR50 response was 40.5% for therapy according to Cochrane network meta- analysis of RCT carried out using methotrexate monotherapy or in combination with csDMARDs, bDMARDs or tofacitinib. Combination DMARD therapy may further improve disease control and successful glucocorticoid tapering compared with monotherapy [34].

6. BIOLOGIC DMARD AS A STEROID SPARING AGENT:

Biologic DMARDs have significantly improved the management of RA by targeting specific inflammatory pathways involved in disease progression. It provides rapid control of disease activity, thereby reducing the steroid dependence. It includes: TNF alpha inhibitors, tocilizumab, abatacept, and rituximab.

TNF ALPHA INHIBITORS

TNF alpha inhibitors include adalimumab, etanercept, infliximab. All these drugs inhibit TNF alpha, which is an inflammatory cytokine found in the joint synovium of RA patients in high concentration [3]. International guidelines recommend the use of glucocorticoids at the lowest dose in the shortest possible duration, with the aim of discontinuation within 3 months. The findings from the international TOCCERRA and PANABA observational studies showed reduction in prednisolone dose. In a French study included 130 patients receiving tocilizumab, found reduction in prednisolone dose. Similarly, in a Danish study with 171 bio-naive patients and a French study with 117 patients starting TNF inhibitors showed reduction in the median dose of 0 mg/day at 52 weeks [35].

Tocilizumab

Tocilizumab acts by binding to IL-6 receptors, which is pro-inflammatory cytokine produced by T and B cells. In moderate to severe active rheumatoid arthritis, it is used in combination with methotrexate. It is given with IV infusion at a dose of 8 mg/ kg. According to the TOZURA clinical trial, glucocorticoid tapering was analyzed at 24 weeks, at which a significant proportion of patients achieved clinical remission based on DAS28 ESR. SEMIRA trial showed that there was an 85% significant reduction in glucocorticoid dose even at 6 months, the tapering occurs from the dose of 5 mg/day to 0 mg/ day [36].

Abatacept

It acts by blocking the activation of T-cells, thereby inhibiting the release of inflammatory cytokines. The result from the SONATA trial, a double-blind RCT, showed a reduction of abatacept from 10 to 5 mg/kg and patients with low DAS28 remission status at 12 months. The dose of abatacept was either 500, 750 or 1000 mg per 4 weeks depending on body weight. These findings showed a gradual reduction in steroid dependence [37].

7. STEROID-SPARING ROLE OF tsDMARDs / JAK INHIBITORS

Janus kinase inhibitors offer a promising class of target DMARDs in treating inflammatory arthritis. JAKs are small molecules that inhibit JAK-STAT intracellular signaling pathways, particularly JAK 1 and JAK 3 [38,39]. These JAK-STATs are involved in immune response and inflammatory cascade. Thereby reducing inflammatory cytokines (IL-6, IFN, GMCSF). EULAR recommends, DAS28-CRP or DAPSA-CRP for disease monitoring [38]. A pilot study showed that 60% of patients tapered the glucocorticoid dose during the treatment period [40]. Another comparative study showed dose reduction from baseline to 3 months was a 0.95mg/ day [41]. Five approved JAK inhibitors including, tofacitinib, baricitinib, upadicitinib, filogitinib and peficitinib, are given as monotherapy or combined with bDMARDs. Among these, Upadicitinib 30 mg and 15 mg showed better efficacy [42]. Real-world data showed a ≥50% reduction in glucocorticoid dose at 4, 12, and 24 weeks [43].

SAFETY CONCERNS OF TOFACITINIB

The FDA requires a warning about an increased risk of serious heart-related events, blood clots, cancer, and death. These warning signs are revised during post-marketing safety trials comparing 5 mg and 10 mg of tofacitinib to anti-TNF. The most often occurring are herpes zoster, TB, and non-melanoma skin cancer. The individual over 65 years old, who had been smoking for the last 5 years increased risk of stroke, cancer, and heart attack [44].

8. NON-PHARMACOLOGICAL AND MULTIDISCIPLINARY APPROACHES

Patient education [45,46,47]

- Educate the patient based on the patient circumstances (comorbidities, disease activity).
- Advice the patients on the hygiene and foot care.
- Provide information about management options and disease.
- Explain about the risk and benefits of treatment options to the patients at which they can easily understand.
- Provide both written and verbal information to the patient about their disease condition and medication adherence.
- Talk to the patient about all the aspects of care throughout the disease duration and respect their decision that they made.
- Recommend general exercise therapy, hydro kinesiotherapy, and joint specific programs.
- Multidisciplinary team approaches should be recommended and it must include rheumatologist, physiotherapist, pharmacist and nurse.

Lifestyle modification

Physician should provide the importance of healthy life style habits including:

- To follow the principles of Mediterranean diet like more vegetables, fruits, bread, less meat and replace cheese and butter products with vegetable oil [46].
- Include regular exercise, smoking cessation, consumption of moderate alcohol, maintaining healthy weight, quality sleep should be promoted while poor sleep exacerbate pain.
- Consume omega 3 fatty acid rich food to relieve symptoms by decreasing the

production of inflammatory prostaglandins and modifying the gut microbiomes [28,47].

- Avoid processed food contain high salts, sugar, butter, oil and animal products which causes inflammation.

Physiotherapy and occupational therapy [46]

- RA patients should provide access to physiotherapy specialist for the periodic review to encourage regular exercise and improve general fitness.
- Learn exercises to enhance muscle strength, joint flexibility and manage other functional impairments.
- Short term pain relief methods include transcutaneous electrical nerve stimulation (TENs) and wax bath.
- Add supplements like vitamin D, multivitamins, cod liver oil to reduce joint inflammation.
- Promote hand exercise programs, if the patient is not on drug regimen for RA or they have been on stable regimen for at least 3 months.
- Psychological intervention: stress management, relaxation, and cognitive coping skills.

Medication adherence

Adherence is generally defined as the extent to which persons behavior in taking medication, following a diet, executing lifestyle changes [48]. Medication adherence is important for preventing disease progression and achieving disease control in RA. Poor adherence to medication including DMARDs, and biologic therapy can lead to increased flare ups, reduced quality of life and joint damage [49].

Factors influencing adherence includes:

- Drug characteristics
- Cognition about illness and medication
- Perceptions
- Demographic and socio-economic factors
- Disease characteristics
- Physician patient relationship
- Educational intervention, counselling and regular follow up can helps to improve adherence and therapeutic outcomes.

Clinical pharmacist role:

Provide patient counselling about:

- Proper drug use.
- Glucocorticoids tapering
- Recognition of adverse reactions
- Importance of adherence
- Medication review helps to identify drug interaction and improve drug safety.
- Helps to monitor adverse effects related with DMARDs, biologics and glucocorticoids.
- Counselling during follow up regarding regular exercise to stretch out muscles, avoid smoking and alcohol, eat healthy diet, regular intake of medication which can improve adherence and treatment outcomes.

9. EMERGING THERAPIES AND FUTURE PERSPECTIVES [50,51]

- **Personalized medicine**

  - Based on patient biomarkers and unique characteristics. New disease modifying antirheumatic drugs and personalized risk predictive models.

  - **Drug delivery systems:** Multipotent mesenchymal stem cells (MSC) act as a vehicle for drug delivery. In this delivery systems, microdevices are developed using nanoparticles, anti- inflammatory drugs and human MSCs.

  - GCSF plays a role in the differentiation and growth of leucocytes and serve as a novel target for RA therapeutics.

- **Biomarkers:** Genetic biomarkers (HLA-DRB1 allele), APRs, MMPS, microRNAs, and novel auto antibodies including anti-CarP and MRP (myeloid related proteins).

  - **Acute phase reactants:** ESR, CRP, serum calprotectin, serum amyloid A, 14-3-3 eta proteins, MMPs (matric metalloproteinases).

  - **Integrating biomarkers:** Multi-biomarker disease activity score (MBDA).

CONCLUSION

Glucocorticoid plays an important role in the management of rheumatoid arthritis due to their rapid anti-inflammatory effects, particularly during bridging therapy and disease flares. However, prolonged use is associated with adverse effects such as weight gain, osteoporosis, cardiovascular complications, increased infection risk, diabetes, and adrenal insufficiency, highlighting the need for effective steroid-sparing strategies. Conventional synthetic DMARDs, biologic DMARDs, and targeted synthetic DMARDs have improved disease control while reducing glucocorticoid dependance. Current approaches focus on early DMARD initiation, disease activity monitoring, treat-to-target principles, and individualized tapering based on patient response. Emerging therapies, including personalized tapering strategies, biomarker-guided treatment, may further improve long-term outcomes. Overall, successful glucocorticoid tapering requires a patient-centered approach that minimizes steroid exposure while maintaining disease control.

REFERENCES

1. Di Matteo A, Bathon JM, Emery P. Rheumatoid arthritis. Lancet. 2023;402(10416):2019-2033. doi:10.1016/S0140-6736(23)01525-8.
2. Pavlov-Dolijanovic S, Bogojevic M, Nozica-Radulovic T, Radunovic G, Mujovic N. Elderly-onset rheumatoid arthritis: characteristics and treatment options. Medicina. 2023 Oct 23;59(10):1878.
3. Walker R. Clinical pharmacy and therapeutics E-Book. Elsevier Health Sciences; 2011 Oct 24.
4. Grassi W, De Angelis R, Lamanna G, Cervini C. The clinical features of rheumatoid arthritis. European journal of radiology. 1998 May 1;27:S18-24.
5. Tang K, Zhu L, Shan S, Luo Z, Zhou J, Ying J, Wu J, Shen G, Song P. Global, regional and national trends in the epidemiology of rheumatoid arthritis from 1990 to 2021: an age-period-cohort effect analysis of the global burden of disease study 2021. RMD open. 2025 Apr 12;11(2).
6. Ma Y, Chen H, Lv W, Wei S, Zou Y, Li R, Wang J, She W, Yuan L, Tao J, Guo X.

Global, regional and national burden of rheumatoid arthritis from 1990 to 2021, with projections of incidence to 2050: a systematic and comprehensive analysis of the Global Burden of Disease study 2021. Biomarker Research. 2025 Mar 24;13(1):47.

7. Papadimitropoulos E, Brnabic A, Vorstenbosch E, Leonardi F, Moyano S, Gomez D. The burden of illness of rheumatoid arthritis in Latin America—A systematic literature review. International journal of rheumatic diseases. 2022 Apr;25(4):405-21.
8. Elsouri KN, Arboleda V, Basbous L, Heiser S, Collins DP, Ragusa P, Baxter C, Cabrera D, Akhand T, Stermer E, Sharma K. Glucocorticoid use in rheumatoid arthritis patients and the onset of pneumonia: a systematic review and meta-analysis. Journal of Osteopathic Medicine. 2023 Mar 24;123(4):179-86.
9. Boers M, Hartman L, Opris-Belinski D, Bos R, Kok MR, Da Silva JA, Griep EN, Klaasen R, Allaart CF, Baudoin P, Raterman HG. Low dose, add-on prednisolone in patients with rheumatoid arthritis aged 65+: the pragmatic randomized, double-blind placebo-controlled GLORIA trial. Annals of the rheumatic diseases. 2022 Jul 1;81(7):925-36.
10. Lee J, Martindale J, Wallace BI, Singh N, Makris UE, Bynum JP. Changes in long-term glucocorticoid use among older adults after new diagnosis of late-onset rheumatoid arthritis. ACR Open Rheumatology. 2025 Mar;7(3):e70013.
11. Long-term clinical outcomes in early rheumatoid arthritis that was treated-to-target in the Best and IMPROVED studies.
12. Dagna L, Feist E, Horneff G, Clemens A, Schuen A, De Benedetti F. Current evidence on switching between biologic therapies for Still's disease: a systematic literature review. In Seminars in Arthritis and Rheumatism 2025 Jul 18 (p. 152789). WB Saunders.
13. Hardy RS, Raza K, Cooper MS. Therapeutic glucocorticoids: mechanisms of actions in rheumatic diseases. Nature Reviews Rheumatology. 2020 Mar;16(3):133-44.
14. Baschant U, Lane NE, Tuckermann J. The multiple facets of glucocorticoid action in rheumatoid arthritis. Nature Reviews Rheumatology. 2012 Nov;8(11):645-55.
15. Hua C, Buttgereit F, Combe B. Glucocorticoids in rheumatoid arthritis: current status and future studies. RMD open. 2020 Jan 7;6(1).
16. Burmester GR, Buttgereit F, Bernasconi C, Álvaro-Gracia JM, Castro N, Dougados M, Gabay C, van Laar JM, Nebesky JM, Pethoe-Schramm A, Salvarani C. Continuing versus tapering glucocorticoids after achievement of low disease activity or remission in rheumatoid arthritis (SEMIRA): a double-blind, multi-centre, randomized controlled trial. The Lancet. 2020 Jul 25;396(10246):267-76.
17. Wang Y, Zhao R, Gu Z, Dong C, Guo G, Li L. Effects of glucocorticoids on osteoporosis in rheumatoid arthritis: a systematic review and meta-analysis. Osteoporosis International. 2020 Aug;31(8):1401-9.
18. Chotiyarnwong P, McCloskey EV. Pathogenesis of glucocorticoid-induced osteoporosis and options for treatment. Nature Reviews Endocrinology. 2020 Aug;16(8):437-47.
19. Kim JW, Jung JY, Kim HA, Suh CH. Anti-Inflammatory effects of low-dose glucocorticoids compensate for their detrimental effects on bone mineral density in patients with rheumatoid arthritis. Journal of Clinical Medicine. 2021 Jun 30;10(13):2944.
20. Li JX, Cummins CL. Fresh insights into glucocorticoid-induced diabetes mellitus and

new therapeutic directions. Nature Reviews Endocrinology. 2022 Sep;18(9):540-57.

21. Soura M, Bakiri A, Fragoulis GE, Vassilakis KD. Glucocorticoid-induced diabetes mellitus: mechanisms, risk factors, and clinical pathways with insights from autoimmune rheumatic diseases. Rheumatology International. 2026 Mar 26;46(4):66.
22. Schattner A. The Cardiovascular burden of rheumatoid arthritis–implications for treatment. The American journal of medicine. 2023 Dec 1;136(12):1143-6.
23. Galati A, Brown ES, Bove R, Vaidya A, Gelfand J. Glucocorticoids for therapeutic immunosuppression: clinical pearls for the practicing neurologist. Journal of the Neurological Sciences. 2021 Nov 15;430:120004.
24. Palmowski A, Nielsen SM, Boyadzhieva Z, Schneider A, Pankow A, Hartman L, Da Silva JA, Kirwan J, Wassenberg S, Dejaco C, Christensen R. Safety and efficacy associated with long-term low-dose glucocorticoids in rheumatoid arthritis: a systematic review and meta-analysis. Rheumatology. 2023 Aug 1;62(8):2652-60.
25. Buttgereit F, Palmowski A. How to taper glucocorticoids in inflammatory rheumatic diseases? A narrative review of novel evidence in rheumatoid arthritis, systemic lupus erythematosus, and giant cell arteritis. Joint Bone Spine. 2022 Jan 1;89(1):105285.
26. Gazitt T, Oren S, Reitblat T, Lidar M, Gurman AB, Rosner I, Halabe N, Feld J, Kassem S, Lavi I, Elkayam O. Treat-to-target concept implementation for evaluating rheumatoid arthritis patients in daily practice. European Journal of Rheumatology. 2019 May 20;6(3):136.
27. Ruderman EM, Nola KM, Ferrell S, Sapir T, Cameron DR. Incorporating the treat-to-target concept in rheumatoid arthritis. Journal of Managed Care Pharmacy. 2012 Nov;18(9 Supp A):1-8.
28. Smolen JS, Landewé RB, Bergstra SA, Kerschbaumer A, Sepriano A, Aletaha D, Caporali R, Edwards CJ, Hyrich KL, Pope JE, De Souza S. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Annals of the rheumatic diseases. 2023 Jan;82(1):3-18.
29. Gaujoux-Viala C, Gossec L. When and for how long should glucocorticoids be used in rheumatoid arthritis? International guidelines and recommendations. Annals of the New York Academy of Sciences. 2014 May;1318(1):32-40.
30. Palmowski A, Pankow A, Terziyska K, Nielsen SM, Christensen R, Bliddal H, Boyadzhieva Z, Buttgereit F. Continuing versus tapering low-dose glucocorticoids in patients with rheumatoid arthritis and systemic lupus erythematosus in states of low disease activity or remission: A systematic review and meta-analysis of randomised trials. InSeminars in Arthritis and Rheumatism 2024 Feb 1 (Vol. 64, p. 152349). WB Saunders.
31. Lau CS, Gibofsky A, Damjanov N, Lula S, Marshall L, Jones H, Emery P. Down-titration of biologics for the treatment of rheumatoid arthritis: a systematic literature review. Rheumatology International. 2017 Nov;37(11):1789-98.
32. Padjen I, Crnogaj MR, Anić B. Conventional disease-modifying agents in rheumatoid arthritis–a review of their current use and role in treatment algorithms. Reumatologia/Rheumatology. 2020 Dec 23;58(6):390-400.
33. Xie W, Huang H, Li G, Hao Y, Gui Y, Wang Y, Deng X, Zhao J, Geng Y, Ji L, Zhang X.

Dynamical trajectory of glucocorticoids tapering and discontinuation in patients with rheumatoid arthritis commencing glucocorticoids with csDMARDs: a real-world data from 2009 to 2020. Annals of the rheumatic diseases. 2021 Aug 1;80(8):997-1003.

34. Giollo A, Fuzzi E, Doria A. Methotrexate in early rheumatoid arthritis: Is the anchor drug still holding?. Autoimmunity reviews. 2022 Apr 1;21(4):103031.
35. Lauper K, Mongin D, Bergstra SA, Choquette D, Codreanu C, Gottenberg JE, Kubo S, Hetland ML, Iannone F, Kristianslund EK, Kvien TK. Oral glucocorticoid use in patients with rheumatoid arthritis initiating TNF-inhibitors, tocilizumab or abatacept: Results from the international TOCERRA and PANABA observational collaborative studies. Joint Bone Spine. 2024 Mar 1;91(2):105671.
36. Choy E, Caporali R, Xavier R, Fautrel B, Sanmarti R, Bao M, Devenport J, Pethö-Schramm A. Effects of concomitant glucocorticoids in TOZURA, a common-framework study programme of subcutaneous tocilizumab in rheumatoid arthritis. Rheumatology. 2019 Jun 1;58(6):1056-64.
37. Bouman CA, Tweehuysen L, Haverkort D, van den Ende CH, van der Maas A, den Broeder AA. Abatacept and tocilizumab tapering in rheumatoid arthritis patients: results of SONATA—a retrospective, exploratory cohort study. Rheumatology Advances in Practice. 2018;2(1):rky008.
38. Conigliaro P, Minerba C, Vendola A, Fiannacca L, Triggianese P, Kroegler B, Greco E, Bergamini A, Chimenti MS. The steroid-sparing effect of JAK inhibitors across multiple patient populations. Frontiers in Immunology. 2024 Apr 12;15:1376476.
39. Dhillon S. Tofacitinib: a review in rheumatoid arthritis. Drugs. 2017 Dec;77(18):1987-2001.
40. Spinelli FR, Garufi C, Mancuso S, Ceccarelli F, Truglia S, Conti F. Tapering and discontinuation of glucocorticoids in patients with rheumatoid arthritis treated with tofacitinib. Scientific reports. 2023 Sep 20;13(1):15537.
41. Adami G, Bixio R, Virelli G, Galvagni I, Mastropaolo F, Morciano A, Ruzzon F, Messina V, Fracassi E, Gatti D, Viapiana O. Glucocorticoid sparing effect of Janus kinase inhibitors compared to biologic disease modifying anti-rheumatic drugs in rheumatoid arthritis, a single-centre retrospective analysis. Rheumatology. 2025 Apr;64(4):1698-704.
42. Cai W, Tong R, Sun Y, Yao Y, Zhang J. Comparative efficacy of five approved Janus kinase inhibitors as monotherapy and combination therapy in patients with moderate-to-severe active rheumatoid arthritis: a systematic review and network meta-analysis of randomized controlled trials. Frontiers in Pharmacology. 2024 Apr 24;15:1387585.
43. Yamane T, Inoue A, Yasuda N, Ohnishi T, Hashiramoto A. Glucocorticoid reduction with baricitinib in rheumatoid arthritis refractory to prior therapies: a 24-week real-world analysis. Frontiers in Medicine. 2026 Mar 19;13:1797242.
44. Food US. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions. (No Title). 2021.
45. Conley B, Bunzli S, Bullen J, O'Brien P, Persaud J, Gunatillake T, Nikpour M, Grainger R, Barnabe C, Lin I. What are the core recommendations for rheumatoid arthritis care? Systematic review of clinical

practice guidelines. Clinical rheumatology. 2023 Sep;42(9):2267-78.

46. guideline NG100 NI. Rheumatoid arthritis in adults: diagnosis and management. National Institute for Health and Care Excellence: London, UK. 2018 Jul.
47. Fraenkel L, Bathon JM, England BR, St. Clair EW, Arayssi T, Carandang K, Deane KD, Genovese M, Huston KK, Kerr G, Kremer J. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis & Rheumatology. 2021 Jul;73(7):1108-23.
48. Lavielle M, Puyraimond-Zemmour D, Romand X, Gossec L, Senbel E, Pouplin S, Beauvais C, Gutermann L, Mezieres M, Dougados M, Molto A. Methods to improve medication adherence in patients with chronic inflammatory rheumatic diseases: a systematic literature review. RMD open. 2018 Jul 27;4(2).
49. Pasma A, van't Spijker A, Hazes JM, Busschbach JJ, Luime JJ. Factors associated with adherence to pharmaceutical treatment for rheumatoid arthritis patients: a systematic review. InSeminars in arthritis and rheumatism 2013 Aug 1 (Vol. 43, No. 1, pp. 18-28). WB Saunders.
50. Sahin D, Di Matteo A, Emery P. Biomarkers in the diagnosis, prognosis and management of rheumatoid arthritis: A comprehensive review. Annals of Clinical Biochemistry. 2025 Jan;62(1):3-21.
51. Jain A, Bishnoi M, Prajapati SK, Acharya S, Kapre S, Singhvi G, Palakurthi S. Targeting rheumatoid arthritis: a molecular perspective on biologic therapies and clinical progress. Journal of Biological Engineering. 2025 Jul 24;19(1):67.

HOW TO CITE: Fathima Nazar, Sajitha G, Glucocorticoid-Sparing Strategies in Rheumatoid Arthritis: Current Approaches and Emerging Therapies, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 6, 7445-7459. https://doi.org/10.5281/zenodo.21053525