New Drug Overview
Rayos® (Prednisone Delayed-Release)

Overview/Summary:
Rayos® (prednisone delayed-release [DR]) is approved by the Food and Drug Administration (FDA) for the treatment of a broad range of conditions including rheumatoid arthritis (RA), polymyalgia rheumatica, psoriatic arthritis, ankylosing spondylitis, asthma and chronic obstructive pulmonary disease.[1] Prednisone is a hormonal steroid in the glucocorticoid subclass. Glucocorticoids have important and profound effects on the body including effects on metabolism, inflammation, immunity and others.[2] Glucocorticoids that are often used in chronic disease management (i.g. prednisone) do not have significant mineralocorticoid, androgenic or estrogenic activity.[3] The actions of glucocorticoids, both natural and synthetic, are primarily achieved by the binding of the nuclear glucocorticoid receptors inside many different types of cells that are distributed throughout the body. Once bound, the glucocorticoid-receptor complex interacts with promoters of target genes and other transcription factors, thus regulating the targeted genes transcription.[2] Generally, it appears that the clinically desirable effects of glucocorticoids results from repression of transcription, leading to a decreased production of proinflammatory proteins.[3] To a lesser degree, glucocorticoids may exert there effect by interacting directly with cell membranes or by binding to certain membrane-bound glucocorticoid receptors.[3] The specific effects that glucocorticoids have on different cells and tissue throughout the body will not be discussed in this review.

The delayed-release formulation consists of a prednisone-containing core tablet encased in an inactive shell. The shell delays the onset of dissolution by approximately four hours after oral administration. This results in prednisone having an increase in the median time to peak plasma concentrations (T_{max}). The DR tablets having a median T_{max} of 6.0 to 6.5 hours compared with 2.0 hours for the immediate-release (IR) formulation.[1] This was developed to counter the high number of proinflammatory cytokines that are produced normally by the body late at night.[4]

Although approved for many indications, studies have only evaluated prednisone DR in adult patients with RA.[5-9] It was shown that prednisone DR significantly reduced the median relative duration of morning stiffness in RA patients by 22.7% while prednisone IR reducing the duration by 0.4% (P=0.045).[5] In addition, a higher proportion of patients who took prednisone DR had a 20% improvement in the signs and symptoms of RA based on American College of Rheumatology criteria (ACR20) compared with placebo.[7]

Table 1. Dosing and Administration

Generic Name (Trade Name)	FDA-Approved Indications	Pediatric Dose	Availability
Prednisone delayed-release	All indications: Tablet: Initial, 5 to 60 mg QD with food*; maintenance, use lowest dosage that will maintain an adequate clinical response; maximum, undefined†	All indications: The recommended dosage should be governed by the same considerations as adults rather than strict adherence to the ratio indicated by age or body weight.	Tablet: 1 mg 2 mg 5 mg

Evidence-based Medicine
- The safety and efficacy of prednisone DR (Rayos®) has been evaluated in several clinical trials.[5-9]
- In the 12-week CAPRA-1 study (N=288), patients with RA who have already been taking a disease modifying antirheumatic drug (DMARD) or other glucocorticoids were assessed. The absolute difference between the treatment groups for change in mean relative duration of morning stiffness was 29.2 min (95% CI, -2.59 to 61.9) in favor of prednisone DR.[5]
    - A 9-month open-label, extension study confirmed continued therapeutic effect over time.[6]

- The CAPRA-2 study (N=350) also assed patients with RA who had previously been receiving either a DMARD or glucocorticoid therapy. This study evaluated the efficacy of prednisone DR using the American College of Rheumatology criteria for RA. The proportion of patients with a 20% improvement in symptoms (ACR20) was significantly higher in the prednisone DR group compared with placebo (48% compared to 29%, P<0.001). The proportion of patients that had at least a 40% improvement in symptoms was also significantly improved with prednisone DR compared with placebo (22% compared to 10%, P<0.006).
- Two observational studies that evaluated 2,975 patients with RA over four or nine months have reaffirmed the results of the phase III clinical trials.[8,9]

Key Points

- According to Current Clinical Guidelines:
    - Widely-accepted criteria for the initiation of glucocorticoid therapy have not been established and current clinical guidelines for the treatment of RA do not address their use.[4,10-13]

- Other Key Facts:
    - Prednisone DR is currently available as a brand-name tablet only; however, prednisone is available generically as an IR tablet and oral solution.
    - Although approved for many indications, studies have only evaluated prednisone DR in adult patients with RA.[1]

References

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New Drug Review
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Overview/Summary

Rayos® (prednisone delayed-release [DR]) is approved by the Food and Drug Administration (FDA) for the treatment of a broad range of conditions including rheumatoid arthritis (RA), polymyalgia rheumatica, psoriatic arthritis, ankylosing spondylitis, asthma and chronic obstructive pulmonary disease.[1] Prednisone is a hormonal steroid in the glucocorticoid subclass. Glucocorticoids have important and profound effects on the body including effects on metabolism, inflammation, immunity and others.[2] Glucocorticoids that are often used in chronic disease management (i.e. prednisone) do not have significant mineralocorticoid, androgenic or estrogenic activity.[3] The actions of glucocorticoids, both natural and synthetic, are primarily achieved by the binding of the nuclear glucocorticoid receptors inside many different types of cells that are distributed throughout the body. Once bound, the glucocorticoid-receptor complex interacts with promoters of target genes and other transcription factors, thus regulating the targeted genes transcription.[2] Generally, it appears that the clinically desirable effects of glucocorticoids results from repression of transcription, leading to a decreased production of proinflammatory proteins.[3] To a lesser degree, glucocorticoids may exert there effect by interacting directly with cell membranes or by binding to certain membrane-bound glucocorticoid receptors.[3] The specific effects that glucocorticoids have on different cells and tissue throughout the body will not be discussed in this review.

The delayed-release formulation consists of a prednisone-containing core tablet encased in an inactive shell. The shell delays the onset of dissolution by approximately four hours after oral administration. This results in prednisone having an increase in the median time to peak plasma concentrations (T_{max}). The DR tablets having a median T_{max} of 6.0 to 6.5 hours compared with 2.0 hours for the immediate-release (IR) formulation.[1] This was developed to counter the high number of proinflammatory cytokines that are produced normally by the body late at night.[4] Prednisone DR is currently available as a brand-name tablet only; however, prednisone is available generically as an IR tablet and oral solution.

Although approved for many indications, studies have only evaluated prednisone DR in adult patients with RA.[5-9] It was shown that prednisone DR significantly reduced the median relative duration of morning stiffness in RA patients by 22.7% while prednisone IR reducing the duration by 0.4% (P=0.045).[5] In addition, a higher proportion of patients who took prednisone DR had a 20% improvement in the signs and symptoms of RA based on American College of Rheumatology criteria (ACR20) compared with placebo.[7] Widely-accepted criteria for the initiation of glucocorticoid therapy have not been established and current clinical guidelines for the treatment of RA do not address their use.[10-13]

Indications

Prednisone DR is FDA-approved as an anti-inflammatory or immunosuppressive agent for certain allergic, dermatologic, gastrointestinal, hematologic, ophthalmologic, nervous system, renal, respiratory, rheumatologic, specific infectious diseases and organ transplant. It is also indicated for the treatment of certain types of endocrine conditions and for palliation of certain neoplastic conditions. Specific diagnoses are summarized in Table 1.

Table 1. Indications[1]

Allergic Conditions*
Atopic dermatitis
Drug hypersensitive reactions
Seasonal or perennial allergic rhinitis
Serum sickness
Dermatologic Diseases
Bullous dermatitis herpetiformis
Contact dermatitis
Exfoliative erythroderma

Mycosis fungoides
Pemphigus
Severe erythema multiforme (Stevens-Johnson syndrome)
Endocrine Conditions
Congenital adrenal hyperplasia
Hypercalcemia of malignancy
Nonsuppurative thyroiditis
Primary or secondary adrenocortical insufficiency[†]
Gastrointestinal Diseases
Crohn's disease, acute episodes
Ulcerative colitis, acute episodes
Hematologic Diseases
Acquired (autoimmune) hemolytic anemia
Diamond-Blackfan anemia
Idiopathic thrombocytopenic purpura in adults
Pure red cell aplasia
Secondary thrombocytopenia in adults
Neoplastic Conditions
Treatment of acute leukemia
Treatment of aggressive lymphomas
Nervous System Conditions
Acute exacerbations of multiple sclerosis
Cerebral edema associated with primary or metastatic brain tumor, craniotomy or head injury
Ophthalmic Conditions
Sympathetic ophthalmia
Uveitis and ocular inflammatory conditions unresponsive to topical steroids
Conditions Related to Organ Transplantation
Acute or chronic solid organ rejection
Pulmonary Diseases
Acute exacerbations of chronic obstructive pulmonary disease (COPD)
Allergic bronchopulmonary aspergillosis
Aspiration pneumonitis
Asthma
Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate chemotherapy
Hypersensitivity pneumonitis
Idiopathic bronchiolitis obliterans with organizing pneumonia
Idiopathic eosinophilic pneumonias
Idiopathic pulmonary fibrosis
Pneumocystis carinii pneumonia (PCP) associated with hypoxemia occurring in an HIV(+) individual who is also under treatment with appropriate anti-PCP antibiotics.
Symptomatic sarcoidosis
Renal Conditions
To induce a diuresis or remission of proteinuria in nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus
Rheumatologic conditions
Acute gouty arthritis[‡]
Ankylosing spondylitis[§]
Dermatomyositis/polymyositis[§]
Polymyalgia rheumatica[§]
Psoriatic arthritis[§]
Relapsing polychondritis[§]
Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low dose

maintenance therapy) §
Sjögren's syndrome§
Systemic lupus erythematosus§
Vasculitis§
Specific Infectious Diseases
Trichinosis with neurologic or myocardial involvement
Tuberculous meningitis with subarachnoid block or impending block used concurrently with appropriate antituberculous chemotherapy

*Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in adults and pediatric populations
†hydrocortisone or cortisone is the first choice: synthetic analogs may be used in conjunction with mineralocorticoids where applicable
‡As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in
§During an exacerbation or as maintenance therapy in selected cases of

Pharmacokinetics[1]

The pharmacokinetic profile of prednisone DR has an approximately 4-hour lag time from that of prednisone IR formulations. The absorption, distribution, and elimination processes are comparable to prednisone IR.

Absorption:

Median T_{max} of prednisone DR was 6.0 to 6.5 hours compared to 2.0 hours for an IR formulation. Subsequently, prednisone was absorbed at the same rate as the IR formulation. Peak plasma concentrations and exposure were comparable for both prednisone IR and prednisone DR administered 2.5 hours after a light meal or with normal meal. Oral absorption of prednisone from prednisone DR was significantly affected by the intake of food. Under standard fasting conditions, both the maximum plasma concentration (C_{max}) and the bioavailability of prednisone DR were significantly lower than under fed conditions, shortly after intake of a high fat meal.

Metabolism

Prednisone is completely converted to the active metabolite prednisolone, which is further metabolized mainly in the liver. The exposure of prednisolone is four to six-fold higher than that of prednisone.

Excretion

Metabolites of prednisone are excreted in the urine as sulfate and glucuronide conjugates. The terminal half-life of both prednisone and prednisolone from the administration of prednisone DR was two to three hours, which is comparable to that from the IR formulation.

Clinical Trials

The safety and efficacy of prednisone DR has been evaluated in several clinical trials.[5-9]

In the 12-week CAPRA-1 study (N=288), adults with active RA, who were receiving disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids, were randomized to treatment with either prednisone DR at bedtime or prednisone IR in the morning. The mean relative change in the duration of morning joint stiffness from baseline was higher with prednisone DR than with prednisone IR (-22.7% compared to -0.4%; difference,22.4%; P,0.045). The absolute difference between the treatment groups was 29.2 min (95% confidence interval [CI], -2.59 to 61.9) in favor of prednisone DR.[5] In the open-label 9-month extension (N=249) study, patients either continued or switched to the prednisone DR treatment. After a total of 12 months of treatment, the duration of morning joint stiffness was reduced by 45% in patients who switched to prednisone DR and by 55% in patients who continued treatment with prednisone DR.[6] The additional reduction in the duration of morning joint stiffness in patients continuing treatment with prednisone DR may in part be due to a placebo effect.[6]

In the 12-week CAPRA-2 study (N=350), adults with active RA, receiving treatment with DMARDs, were randomized to treatment with either prednisone DR at bedtime or placebo. Compared to placebo, treatment with prednisone DR produced higher response rates based on the American College of

Rheumatology criteria. The proportion of patients with a 20% improvement in signs and symptoms of RA (ACR20) was 48% in the prednisone DR group compared to 29% in the placebo group (P<0.001). The proportion of patients with a 50% improvement in signs and symptoms (ACR50) was also significantly higher in the prednisone delayed-release group (22% vs 10%; P<0.006). The duration of morning stiffness was decreased by a median of 20 min compared to placebo (95% CI, 7 to 32).[1,7]

Two observational studies that evaluated 2,975 patients with RA over four or nine months have reaffirmed the results of the phase III clinical trials.[8,9]

Table 2. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Buttgereit et al[5] (CAPRA-1) Prednisone DR QHS vs prednisone IR QAM Doses were taken to achieve the appropriate dose of 3 to 10 mg daily.	AC, DB, MC, PG, RCT Patients 18 to 80 years old with RA, receiving DMARDs and glucocorticoids for ≥3 months, morning stiffness ≥45 minutes, daily maximum pain intensity score (100 mm VAS) ≥30 mm, ≥3 painful joints, ≥1 swollen joints, and signs of inflammatory processes (ESR ≥28 mm), or CRP >1.5 times the upper limit of the normal range.	N=288 12 weeks	Primary: Change in morning stiffness of the joints (relative) Secondary: Changes in DAS28, recurrence of joint stiffness during the day, pain intensity, quality of sleep, HAQ-DI, SF36 scores, CRP, ESR, osteocalcin, IL-6	Primary: The mean relative change in duration of morning stiffness of the joints from baseline to end of treatment was higher with prednisone DR than with prednisone IR (-22.7% vs -0.4%; difference=22.4% [95% CI, 0.49 to 44.30]; P=0.045). The absolute difference between the treatment groups was 29.2 min in favor of prednisone DR (95% CI, -2.59 to 61.9; P=0.072). Secondary: After 12 weeks of treatment, no clinically relevant differences were observed between the two treatment groups for almost all secondary variables (DAS28, recurrence of joint stiffness during the day, pain intensity, quality of sleep, HAQ-DI, SF36 scores, CRP, erythrocyte sedimentation rate and osteocalcin). The exception being IL-6, which had a significant decrease in the prednisone DR group but remained constant in the IR group (P=0.0322).
Buttgereit et al[6] Prednisone DR QHS	ES, MC, OL All patients who completed the double-blind study (CAPRA-1)[2] and did not develop any exclusion criteria	N=249 9 months	Primary: Absolute and relative reductions in duration of morning stiffness of the joints, changes in IL-6 plasma levels, DAS28, pain intensity and ACR20 improvement Secondary: Not reported	Primary: After 6 months of treatment (or 3 months of open-label period), the duration of morning stiffness was reduced by 54% in patients who switched to prednisone DR and by 56% in patients who continued treatment with prednisone DR. After 12 months of treatment (or 9 months of open-label period), the duration of morning stiffness was reduced by 45% in patients who switched to prednisone DR and by 55% in patients who continued treatment with prednisone DR. The mean absolute reductions in the duration of morning stiffness were 88±128.3 min (from 182±127.4 min at baseline) in patients who switched

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				to prednisone DR and 83±83.7 min (from 156±97.3 min at baseline) in patients who continued therapy with prednisone DR. After 9 months of open-label period, plasma levels of IL-6 declined by 46.4% in patients who switched to prednisone DR, while low levels of IL-6 were sustained in patients who continued therapy with prednisone DR (P<0.05). After 9 months of open-label period, treatment with prednisone DR resulted in statistically significant improvements (P<0.05) compared to baseline in DAS28 and VAS of pain intensity in patients who switched to prednisone DR and those who continued therapy with prednisone DR. Of the 219 patients who completed the entire 12-month study, 37% achieved an ACR20 response. Secondary: Not reported
Buttgereit et al[7] (CAPRA-2) Prednisone DR 5 mg QHS vs placebo	DB, MC, PC, RCT Patients 18 to 80 years old with RA, receiving DMARDs for ≥6 months, morning stiffness ≥45 minutes on ≥4 days within the 7 days of screening and a swollen joint count of ≥4 and a tender joint count of ≥4.	N=350 12 weeks	Primary: Proportion of patients with an ACR20 response at week 12 Secondary: ACR50 and ACR70 responses, change in duration of morning stiffness between baseline and week 12, DAS28, morning and evening pain, tender and swollen joint count, FACIT-F and SF-36	Primary: At week 12, 48% of patients receiving prednisone DR achieved an ACR20 response compared with 29% in the placebo group, for a difference of 19% (P<0.001). Secondary: A greater proportion of patients receiving prednisone DR achieved ACR50 response (22% vs 10%; P<0.006) and ACR70 response (7% vs 3%; P<0.10) than placebo at week 12. At week 12, the median decrease in the duration of morning stiffness was 55 min in the prednisone DR group, compared with 33 min with placebo (median difference: 20 min (95% CI, 7 to 32). Treatment with prednisone DR resulted in significant increases in the proportion of patients achieving low disease activity (DAS28 ≤3.2) after 6 weeks (P<0.001) and 12 weeks (P=0.0109) of treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				At 12 weeks, 11.3% patients in the prednisone DR group achieved a DAS28 score <2.6 (disease remission or minimal disease activity) compared with 6.7% with placebo. Compared to placebo at 12 weeks, treatment with prednisone DR resulted in greater reductions in morning pain (P=0.012) and evening pain (P=0.049). Compared to placebo at 12 weeks, treatment with prednisone DR resulted in statistically significant decreases in the tender join count (P=0.001), swollen join count (P=0.009), FACIT-F score (P=0.003), SF-36 physical component Score (P<0.001); however, increase in SF-36 mental component score was not statistically significant (P=0.14).

Drug regimen abbreviations: DR=delayed-release, HS=bedtime, IR=immediate-release, QAM=daily in the morning, QHD=daily at bedtime
Study abbreviations: AC=active control, CI=confidence interval, DB=double blind, ES=extension study, ITT=intention-to-treat population, MC=multicenter, OL=open label, OS=observational study, PC=placebo controlled, PG=parallel group, PPP=per-protocol population, RCT=randomized controlled trial
Miscellaneous abbreviations: 6M=6-methyl, ACR=American College of Rheumatology, ACR20/50/70=20/50/70% improvement in RA signs and symptoms according to ACR criteria, CRP=C-reactive protein, DAS28=28-joint disease activity score, DMARD=disease-modifying antirheumatic drug, ESR=erythrocyte sedimentation rate, EULAR=European League Against Rheumatism, FACIT-F=functional assessment of chronic illness therapy-fatigue, HAQ-DI=health assessment questionnaire disability index, IL-6=interleukin 6, NRS=Numerical Rating Scale, QAS=Questionnaire on Activity Status, RA=rheumatoid arthritis, SF36=Short-Form 36 questionnaire, VAS=visual analogue scale

Special Populations

Table 3. Special Populations[1,14]

Special Population	Recommendations
Elderly	No overall differences in safety or effectiveness were observed between elderly patients and younger adult patients. Other reported clinical experience with prednisone has not identified differences in responses between the elderly and younger patients. The incidence of corticosteroid-induced side effects may be increased in geriatric patients and are dose-related. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy, especially in elderly with reduced renal function.
Children	The efficacy and safety of prednisone in the pediatric population are based on the well-established course of effect of corticosteroids which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (>2 years of age), and aggressive lymphomas and leukemias (>1 month of age). Pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis.
Renal Dysfunction	Not studied in renal dysfunction. Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.
Hepatic Dysfunction	Not studied in hepatic dysfunction. Specific guidelines for dosage adjustments in renal impairment are not available; prednisone is converted to its active metabolite by the liver. Use of oral prednisolone over oral prednisone may be preferred in patients with significant hepatic dysfunction.
Pregnancy	Pregnancy Category D. Multiple cohort and case controlled studies in humans suggest that maternal corticosteroid use during the first trimester increases the rate of cleft lip with or without cleft palate from about 1/1000 infants to 3 to 5/1000 infants. Two prospective case control studies showed decreased birth weight in infants exposed to maternal corticosteroids in utero.
Nursing Mothers	Yes (0.14%) Prednisolone, the active metabolite of prednisone, is secreted in human milk. The risk of infant exposure to prednisolone through breast milk should be weighed against the known benefits of breastfeeding for both the mother and baby.

Adverse Drug Events

The safety of prednisone DR was evaluated in two clinical studies involving 375 patients (aged 20 to 80 years) with rheumatoid arthritis. The clinical trial experience did not raise new safety concerns beyond those already established for immediate-release prednisone. Specific frequencies of adverse reactions were not provided in the FDA-approved label. Common adverse reactions for corticosteroids include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.[1]

Contraindications

Prednisone DR is contraindicated in patients with known hypersensitivity to prednisone or to any of the excipients. Use of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.[1]

Warnings/Precautions

Table 4. Warnings and Precautions[1]

Warning/Precaution	Prednisone delayed-release
Acute myopathy, generalized has been observed with high-dose corticosteroids	✔
Adrenocortical insufficiency associated with withdrawal or rapid discontinuation of corticosteroids; gradually reduce dose when discontinuing.	✔
Alterations in cardiovascular/renal function; elevation of blood pressure, salt, and water retention, and increased excretion of potassium and calcium may occur. Dietary salt restriction and potassium supplementation may be necessary. Use with caution in patients with congestive heart failure, hypertension, or renal insufficiency.	✔
Behavior and mood disturbance, including euphoria, insomnia, mood swings, personality changes, severe depression and psychosis have been reported.	✔
Bone density decreased; may lead to the development of osteoporosis at any age; use caution in patients at an increased risk for developing osteoporosis. Monitor bone density in patients with long-term corticosteroid use.	✔
Endocrine function changes (reversible); hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome and hyperglycemia. Monitor patients with chronic administration.	✔
Gastrointestinal perforation risk increased in patients with certain gastrointestinal disorders; use with caution if there is a probability of impending perforation, abscess, or other pyogenic infections; diverticulitis; fresh intestinal anastomoses; and active or latent peptic ulcer.	✔
Growth and development in children may be negatively impacted with long-term corticosteroid use; monitor carefully.	✔
Infection risk increased, including viral, bacterial, fungal, protozoan, or helminthic infections, especially when given at high doses.	✔
Kaposi's sarcoma has been reported in patients receiving corticosteroids, most often for chronic conditions; discontinuation may result in clinical improvement.	✔
Ophthalmic effects; prolonged use of corticosteroids may produce cataracts, glaucoma with possible damage to the optic nerves. If corticosteroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored. Corticosteroids should not be used in active ocular herpes simplex	✔
Vaccination with live or live, attenuated vaccines should not be done in patients receiving immunosuppressive doses of corticosteroids; responses to killed or inactivated vaccines cannot be predicted, but may be done.	✔

Drug Interactions

Table 5. Drug Interactions[1]

Generic Name	Interacting Medication or Disease	Potential Result
Corticosteroids	Amphotericin B	Case reports of cardiac enlargement and congestive heart failure with concurrent hydrocortisone use.
Corticosteroids	Anticholinesterase agents	Concomitant use may produce severe weakness in patients with myasthenia gravis. If possible, discontinue anticholinesterase agents at least 24 hours before initiating corticosteroid therapy.
Corticosteroids	Antidiabetics	Blood glucose increased with corticosteroid use; dose adjustment may be required.
Corticosteroids	CYP3A4 inducers	Decreased corticosteroid concentrations, may require increased dose of corticosteroids with concomitant use.
Corticosteroids	CYP3A4 inhibitors	Increased corticosteroid concentrations, may require decrease in dose of corticosteroids with concomitant use
Corticosteroids	Cholestyramine	Decreased concentration of corticosteroids (increased clearance of corticosteroids).
Corticosteroids	Cyclosporine	Increased activity of both cyclosporine and corticosteroids. Convulsions have been reported with concurrent use.
Corticosteroids	Digitalis (digoxin)	May be at increased risk of arrhythmias due to hypokalemia
Corticosteroids	Estrogens	Increased effect of corticosteroids (decreased hepatic metabolism of corticosteroids)
Corticosteroids	Isoniazid	Decreased isoniazid concentrations.
Corticosteroids	NSAIDs	Increased risk of gastrointestinal side effects.
Corticosteroids	Potassium-depleting agents	Monitor closely for development of hypokalemia.
Corticosteroids	Skin tests	Corticosteroids may suppress reaction to skin tests.
Corticosteroids	Toxoids and Live or Attenuated Vaccines	Patients on corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible.
Corticosteroids	Warfarin	Inhibition of response to warfarin; monitor frequently.

CYP=cytochrome P-450, NSAID=nonsteroidal anti-inflammatory drug

Dosage and Administration

Prednisone DR tablets should be administered orally with food. The tablets should not be broken, divided, or chewed due to coating that allows for the delayed-release action. Dosage of prednisone delayed-release should be individualized according to disease, disease severity and the patient response. For pediatric patients, the recommended dosage should be governed by the same considerations rather than strict adherence to the ratio indicated by age or body weight. When deciding the administration time for the delayed-release tablets, consider the pharmacokinetics and the disease or condition being treated. Prednisone is released from the tablet beginning approximately four hours after intake of the first dose. Dose comparisons showing equivalent milligram dosages for various glucocorticoids is summarized in Table 7.[1]

Table 6. Dosing and Administration[1]

Generic Name	Adult Dose	Pediatric Dose	Availability
Prednisone delayed-release	All indications: Tablet: Initial, 5 to 60 mg QD with food*; maintenance, use lowest dosage that will maintain an adequate clinical response; maximum, undefined†	All indications: The recommended dosage should be governed by the same considerations as adults rather than strict adherence to the ratio indicated by age or body weight.	Tablet: 1 mg 2 mg 5 mg

QD=daily
*Although not specifically recommended in the label, prednisone delayed-release is normally given at bedtime to coordinate the delivery of prednisone with circadian biological rhythms.
†No absolute maximum dosage; the Boston Collaborative Drug Study found that psychiatric events occurred in fewer than 1% of patients when prednisone was prescribed in doses of 30 mg/day or less, whereas the incidence rose to 18% in patients receiving 80 mg/day[14,15]

Table 7. Glucocorticoid Equivalent Doses[1]

Glucocorticoid	Equivalent Dose	Glucocorticoid	Equivalent Dose
Betamethasone	0.75 mg	Paramethasone	2 mg
Cortisone	25 mg	Prednisolone	5 mg
Dexamethasone	0.75 mg	Prednisone	5 mg
Hydrocortisone	20 mg	Triamcinolone	4 mg
Methylprednisolone	4 mg		

Clinical Guidelines

Table 8. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Rheumatology: **2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis (2012)**[11]	Initiating and switching among DMARDs • If a patient deteriorates from low to moderate/high disease activity after three months of DMARD monotherapy (in patients without poor prognostic features), then methotrexate, hydroxychloroquine, or leflunomide should be added. • Add another non-methotrexate DMARD or switch to a different non-methotrexate DMARD if the patient still experiences moderate or high disease activity following three months of methotrexate or methotrexate/DMARD combination therapy. Switching from DMARDs to biologic agents • For patients with continued moderate or high disease activity following three months of methotrexate monotherapy or DMARD combination therapy, an alternative to DMARD therapy is adding or changing therapy to a TNF-α inhibitor, abatacept or rituximab. • Add or switch to a TNF-α inhibitor if a patient continues to have moderate or high disease activity, following three months of intensified DMARD combination therapy or after a second DMARD has been tried. Switching among biologic agents due to lack of benefit or loss of benefit • In patients with moderate or high disease activity despite three months of TNF-α inhibitor therapy due to a lack or loss of benefit, switching to another TNF-α inhibitor or a non-TNF-α inhibitor biologic is recommended. • In patients with moderate or high disease activity despite six months of a non-TNF-α inhibitor biologic and the failure is due to a lack or loss of

Clinical Guideline	Recommendations
	benefit, the patient should switch to another non-TNF-α inhibitor biologic or a TNF-α inhibitor. Switching among biologic agents due to harms/adverse events • Patients with high disease activity following treatment failure of a TNF-α inhibitor due to a serious adverse event, an attempt should be made to switch to a non-TNF-α inhibitor biologic. • In patients with moderate or high disease activity after failing an TNF-α inhibitor because of a nonserious adverse event, switch to another anti-TNF-α inhibitor or a non-TNF-α inhibitor biologic. • Patients with moderate or high disease activity after failing a non-TNF-α inhibitor biologic because of an adverse event (serious or nonserious) should be switched to another non-TNF-α inhibitor biologic or a TNF-α inhibitor. Biologic use in Hepatitis B or C • Etanercept could potentially be used in rheumatoid arthritis patients with hepatitis C requiring rheumatoid arthritis treatment; however, biologic agents should not be used in rheumatoid arthritis patients with untreated chronic hepatitis B and in rheumatoid arthritis patients with treated chronic hepatitis B with Child-Pugh class B and higher. Malignancies • Patients treated for solid malignancies more than five years ago or who have been treated for nonmelanoma skin cancer more than five years ago, treatment with a biologic agent may be initiated or continued if the patient would otherwise qualify for biologic therapy. • Rituximab should only be started or initiated in rheumatoid arthritis patients with a previously treated solid malignancy within the last five years, a previously treated nonmelanoma skin cancer within the last five years, a previously treated melanoma skin cancer, or a previously treated lymphoproliferative malignancy. • Little is known about the effects of biologic therapy in patients with a history of a solid cancer within the past five years. Congestive heart failure • Anti-TNF biologic in rheumatoid arthritis patients with congestive heart failure is not recommended in those with a New York Heart Association class III or IV and who have an ejection fraction of 50% or less.
European League Against Rheumatism: **EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. (2013)**[12]	• Treatment of rheumatoid arthritis must be based on a shared decision between the patient and the rheumatologist. • Rheumatoid arthritis incurs high individual, societal and medical costs, all of which should be considered in its management. • Therapy with DMARDs should be started as soon as the diagnosis of rheumatoid arthritis is made. • Treatment should be aimed at reaching a target of remission or low disease activity in every patient. • Methotrexate should be part of the first treatment strategy in patients with active rheumatoid arthritis. • If methotrexate is contraindicated or is not tolerated, treatment with sulfasalazine or leflunomide should be considered. • In DMARD-naïve patients, treatment with conventional synthetic DMARD monotherapy or combination therapy of conventional synthetic DMARDs is

Clinical Guideline	Recommendations
	recommended. • Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more conventional synthetic DMARDs) for up to six months, but should be tapered as rapidly as clinically feasible. • If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another conventional synthetic DMARD strategy should be considered; when poor prognostic factors are present, addition of a biologic DMARD should be considered. • In patients with inadequate response to methotrexate and/or other conventional synthetic DMARDs, biologic DMARDs (TNF-α inhibitors, abatacept or tocilizumab) should be commenced with methotrexate; treatment with rituximab may be considered in the patients with recent history of lymphoma, latent tuberculosis with contraindications to the use of chemoprophylaxis, living in a tuberculosis-endemic region, or a previous history of demyelinating disease. • If a first biologic DMARD has failed, patients should be treated with another biologic DMARD; if a first TNF-α inhibitor therapy has failed, patients may receive another TNF-α inhibitor or a biological agent with a different mechanism of action. • Given the paucity of clinical experience and long-term safety data, tofacitinib should primarily be used when biological treatment has failed; additional clinical experience and safety data from registries, with a particular focus on serious infections, herpes zoster and malignancies, will be needed before the place of tofacitinib in the treatment sequence can be clarified. • If a patient is in persistent remission after having tapered glucocorticoids, tapering of biologic DMARDs can be considered, especially if this treatment is combined with a conventional synthetic DMARD. • In cases of sustained long-term remission, cautious reduction of the conventional synthetic DMARD dose could be considered, as a shared decision between patient and physician.
National Institute for Health and Clinical Excellence: **Rheumatoid Arthritis National Clinical Guideline for Management and Treatment in Adults (2009)**[13]	• In people with newly diagnosed active rheumatoid arthritis, offer a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as first-line treatment as soon as possible, ideally within three months of the onset of persistent symptoms. • In people with recent-onset rheumatoid arthritis receiving combination DMARD therapy and in whom sustained and satisfactory levels of disease control have been achieved, cautiously try to reduce drug doses to levels that still maintain disease control. • In people with newly diagnosed rheumatoid arthritis for which combination DMARD therapy is not appropriate, start DMARD monotherapy; placing greater emphasis on fast escalation to a clinically effective dose rather than on the choice of DMARD. • In people with established rheumatoid arthritis whose disease is stable, cautiously reduce dosages of disease modifying or biological drugs. Return promptly to disease-controlling dosages at the first sign of a flare. • When introducing new drugs to improve disease control into the treatment regimen of a person with established rheumatoid arthritis, consider decreasing or stopping their pre-existing rheumatological drugs once the disease is controlled. • In any person with established rheumatoid arthritis in whom disease-modifying or biological drug doses are being decreased or stopped,

Clinical Guideline	Recommendations
	arrangements should be in place for prompt review. • Consider offering short-term treatment with glucocorticoids (oral, intramuscular or intra-articular) to rapidly improve symptoms in people with newly diagnosed rheumatoid arthritis if they are not already receiving glucocorticoids as part of DMARD combination therapy. • Offer short-term treatment with glucocorticoids for managing flares in people with recent onset or established disease, to rapidly decrease inflammation. • In people with established rheumatoid arthritis, only continue long-term treatment with glucocorticoids when the long-term complications of glucocorticoid therapy have been fully discussed, and all other treatment options (including biological drugs) have been offered. • On the balance of its clinical benefits and cost effectiveness, anakinra is not recommended for the treatment of rheumatoid arthritis, except in the context of a controlled, long-term clinical study. • Patients currently receiving anakinra for rheumatoid arthritis may suffer loss of wellbeing if their treatment were discontinued at a time they did not anticipate. Therefore, patients should continue therapy with anakinra until they and their consultant consider it is appropriate to stop. • Do not offer the combination of TNF-α inhibitor therapy and anakinra for rheumatoid arthritis. • Oral NSAIDs or COX-2 inhibitors should be used at the lowest effective dose for the shortest possible period of time. • When offering treatment with an oral NSAID or COX-2 inhibitor, the first choice should be either a standard NSAID or a COX-2 inhibitor. In either case, these should be co-prescribed with a proton pump inhibitor, choosing the one with the lowest acquisition cost. • All oral NSAIDs or COX-2 inhibitors have analgesic effects of a similar magnitude but vary in their potential gastrointestinal, liver and cardio-renal toxicity; therefore, when choosing the agent and dose, healthcare professionals should take into account individual patient risk factors, including age. When prescribing these drugs, consideration should be given to appropriate assessment and/or ongoing monitoring of these risk factors. • If a person with rheumatoid arthritis needs to take low-dose aspirin, healthcare professionals should consider other analgesics before substituting or adding an NSAID or COX-2 inhibitor (with a proton pump inhibitor) if pain relief is ineffective or insufficient. • If NSAIDs or COX-2 inhibitors are not providing satisfactory symptom control, review the disease-modifying or biological drug regimen. • The TNF-α inhibitors adalimumab, etanercept and infliximab are recommended as options for the treatment of adults who have both of the following characteristics: o Active rheumatoid arthritis as measured by disease activity score (DAS 28) >5.1 confirmed on at least two occasions, one month apart. o Have undergone trials of two DMARDs, including methotrexate (unless contraindicated). A trial of a DMARD is defined as being normally of six months, with two months at standard dose, unless significant toxicity has limited the dose or duration of treatment. • TNF-α inhibitors should normally be used in combination with methotrexate. Where a patient is intolerant of methotrexate or where methotrexate treatment is considered to be inappropriate, adalimumab and

Clinical Guideline	Recommendations
	etanercept may be given as monotherapy. • Treatment with TNF-α inhibitors should be continued only if there is an adequate response at six months following initiation of therapy. An adequate response is defined as an improvement in DAS 28 of 1.2 points or more. • After initial response, treatment should be monitored no less frequently than six-monthly intervals with assessment of DAS 28. Treatment should be withdrawn if an adequate response is not maintained. • An alternative TNF-α inhibitor may be considered for patients in whom treatment is withdrawn due to an adverse event before the initial six-month assessment of efficacy provided the risks and benefits have been fully discussed with the patient and documented. • Escalation of dose of the TNF-α inhibitors above their licensed starting dose is not recommended. • Treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose and product price per dose). This may need to be varied in individual cases due to differences in the mode of administration and treatment schedules. • Use of the TNF-α inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended. • Initiation of TNF-α inhibitors and follow-up of treatment response and adverse events should be undertaken only by a specialist rheumatological team with experience in the use of these agents.

Conclusions

Prednisone DR (Rayos®) is used as an anti-inflammatory or immunosuppressive agent for certain allergic, dermatologic, gastrointestinal, hematologic, ophthalmologic, nervous system, renal, respiratory, rheumatologic, specific infectious diseases and organ transplant. It is also indicated for the treatment of certain types of endocrine conditions and for palliation of certain neoplastic conditions.[1] As a glucocorticoid, it has profound effects throughout the body.[2,3] The delayed-release formulation consists of a prednisone-containing core tablet encased in an inactive shell which delays the onset of dissolution by approximately four hours after oral administration. The delayed release formulation of prednisone was developed to counter the high number of proinflammatory cytokines that are produced normally by the body late at night.[4] Because of this, prednisone DR must be taken at bedtime and should be administered with food.[1] While prednisone is available generically as an IR tablet and oral solution, prednisone DR is currently available as a brand-name tablet only.

Prednisone DR, as mentioned above, carries many FDA-approved indications. However, clinical trials of the delayed-release formulation only evaluated the agent in adult patients with RA.[5-9] It was shown that prednisone DR significantly reduced the median relative duration of morning stiffness in RA patients by 22.7% while prednisone IR reducing the duration by 0.4% (P=0.045).[5] In addition, a higher proportion of patients who took prednisone DR had a 20% improvement in the signs and symptoms of RA based on American College of Rheumatology criteria (ACR20) compared with placebo.[7] Widely-accepted criteria for the initiation of glucocorticoid therapy have not been established and current clinical guidelines for the treatment of RA do not address their use.[10-13]

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