Rayos: A Novel Oral Delayed-Release Prednisone for the Treatment of Rheumatoid Arthritis and Other Inflammatory Diseases

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Rheumatic conditions comprise a broad spectrum of more than 100 different diseases that affect approximately 50 million Americans. Some of these diseases are seen frequently, such as rheumatoid arthritis (RA) and gout, and others are relatively rare, including relapsing polychondritis and polymyalgia rheumatica. The most familiar rheumatic diseases affect the muscles, joints, and bones, and cause chronic joint pain, swelling, stiffness, and fatigue. But rheumatic diseases can also affect other organs and organ systems, including the heart, eyes, lungs, nervous system, blood, vascular system, and skin. Inflammatory rheumatic diseases—RA, lupus, and gout—are the most severe of these conditions and can destroy joints and organs, causing severe pain, disability, and even death.

Without appropriate treatment, rheumatic diseases can exacerbate other serious coexisting diseases and infections. For example, one third of lupus-related deaths result from serious infections, and the risk for myocardial infarction is 60% higher in patients with RA than in the general population.

The Burden and Impact of Rheumatic Diseases
Rheumatic diseases can occur in the prime of life and can be painful, disabling, life-changing, and costly. More than 7 million people in the United States have inflammatory, autoimmune rheumatic diseases; of these, 1.3 million adults have RA; 300,000 children have juvenile idiopathic arthritis; between 161,000 and 322,000 adults have systemic lupus erythematosus; between 0.4 million and 3.1 million adults have Sjogren’s syndrome; approximately 300,000 adults have psoriatic arthritis; and 3 million adults have gout.

Less common rheumatic diseases include polymyalgia rheumatica, affecting approximately 711,000 adults; ankylosing spondylitis, affecting 129 of every 100,000 persons; polymyositis, affecting 13,500 persons; and relapsing polychondritis, which involves approximately 600 cases in the United States.

These diseases are difficult and costly to treat. Complex treatment regimens may be required, and the total annual cost is in the billions of dollars in the United States. In 2006, the medical cost of RA and other rheumatic diseases was $127.8 billion, which exceeded the estimated cost of cancer care by nearly $24 billion.

RA and rheumatic diseases are currently the leading cause of disability in the United States, accounting for 19% of disability, with back or spine problems representing a close second, at 17%.

RA can interfere with the ability to work and can lead to mental and emotional problems. In addition, RA can affect different aspects of cognition.

FDA Approves Rayos for Multiple Indications
Delayed-release prednisone (Rayos, Horizon Pharma) was approved by the US Food and Drug Administration (FDA) on July 26, 2012, for the treatment of a broad range of inflammatory-mediated diseases, including rheumatic, respiratory, dermatologic, allergic, endocrine, and hematologic diseases.

The rationale for the development of Rayos rests on chronobiological observations in patients with inflammatory-mediated diseases. The delayed-release system is engineered to address the circadian rhythm of endogenous cortisol and disease symptoms, which reach their peak levels in the early morning hours. Routine morning administration of conventional prednisone does not achieve adequate control of cortisol levels and disease symptoms, but taking delayed-release prednisone at bedtime releases glucocorticoid (ie, prednisone) 4 hours later, in the early morning hours, which improves symptom control.

With the recent FDA approval of Rayos, the manufacturer will initially be focusing its marketing efforts on the use of the drug in RA and in polymyalgia rheumatica, and then will be expanding the focus to 6 key inflammatory diseases—RA, polymyalgia rheumatica, psoriatic arthritis, ankylosing spondylitis, asthma, and chronic obstructive pulmonary disease (COPD). These 6 diseases are mediated by interleukin (IL)-6.

The Burden and Impact of Asthma and COPD
Nearly 25 million Americans suffer from asthma—approximately 8% of all adults and more than 9% of all children. The prevalence of asthma has increased across all age-, sex, and ethnic groups. Asthma accounts for approximately 497,000 hospitalizations annually in the United States and is responsible for more than 10 million missed workdays for adults.
and nearly 13 million missed school days among children. Asthma is managed with appropriate treatment and patient education.

The annual cost of asthma is nearly $18 billion in the United States. Direct costs account for approximately $10 billion, and indirect costs account for approximately $8 billion. Asthma causes more than 3000 deaths in the United States annually and is a contributing factor for approximately 7000 additional deaths annually.

COPD is a progressive disease that interferes with the ability to breathe. Smoking is the leading cause of COPD; other causes include exposure to environmental lung irritants, and possibly air pollution. Currently, more than 12 million Americans have been diagnosed with COPD, and another 12 million may have the disease but have not been formally diagnosed. COPD is a major cause of disability, and this disease is the third leading cause of death in the United States. In 2002, the direct medical costs of COPD in the United States were estimated at $18 billion, and indirect costs associated with morbidity and mortality were approximately $14.1 billion. In 2004, approximately 25% of all cases of dyspnea presenting to the emergency department were related to exacerbations of COPD. In 2000, COPD was responsible for 15 million physician office visits and 1.5 million visits to the emergency department.

Phase 3 Clinical Trials
The 2 pivotal clinical trials that led to the FDA approval of Rayos were conducted in patients with RA. The trials are known as CAPRA (Circadian Administration of Prednisone in Rheumatoid Arthritis)-1 and CAPRA-2.

CAPRA-1
CAPRA-1 was a 12-week, multicenter, randomized, double-blind trial conducted at 17 centers in Germany and 12 in Poland between August 2004 and April 2006. After a 2-week screening phase, patients with active RA were randomized to the oral delayed-release prednisone (N = 144) or to oral immediate-release prednisone (N = 144). The delayed-release tablet was taken at bedtime and released active prednisone 4 hours later. Immediate-release prednisone was administered in the morning. The double-blind treatment phase entailed study visits at baseline (week 0) and after 2, 6, and 12 weeks of treatment. At the end of the double-blind phase, patients were offered delayed-release prednisone in a 9-month open study phase.

Disease activity was assessed by the 28-joint Disease Activity Score (DAS28) at all visits. Health status was assessed using the Health Assessment Questionnaire (HAQ) at visits 1, 2, and 5, and using the 36-item Short-Form Health Survey (SF-36) at visits 1 and 5. Laboratory measures were analyzed. During the double-blind phase, treatment with other disease-modifying antirheumatic drugs (DMARDs) and with nonsteroidal anti-inflammatory drugs (NSAIDs) had to be kept constant. The use of other therapies was not allowed.

The primary end point of CAPRA-1 was the relative change from baseline in duration of morning stiffness at the end of the 12-week double-blind phase. Secondary efficacy outcomes included recurrence of joint stiffness, pain intensity each day, quality of sleep, DAS28 score, physician’s global assessment of disease activity, laboratory values, HAQ disability index, and SF-36 scores.

Patient Population
A total of 288 male and female patients (aged 18-80 years) with active disease and a documented history of RA according to American College of Rheumatology (ACR) criteria were enrolled in CAPRA-1. In general, participants were older and predominantly female, which is similar to the population treated in clinical practice. Patients randomized to immediate-release prednisone had a longer duration of morning stiffness of the joints than patients taking the delayed-release prednisone. Approximately 40% of the patients had disease duration of more than 10 years.

Efficacy
The mean relative change in the duration of morning stiffness of joints from baseline to the end of 12 weeks
was significantly higher with delayed-release prednisone than with immediate-release prednisone, –22.7% versus –0.4%, respectively, reflecting a difference (rounded to the nearest tenth) of 22.4% (P = .045). The patients treated with the delayed-release prednisone achieved a mean reduction of 44 minutes from baseline, with an absolute between-group difference of 29.2 minutes favoring delayed-release prednisone.19

After 2 weeks of treatment, morning stiffness of the joints was improved more in the delayed-release prednisone group, with a difference of approximately 10%. The between-group difference continued to increase with longer treatment and reached a plateau of approximately 38% from week 7 until the end of the treatment period.19

No clinically relevant differences were observed for other secondary efficacy end points, with the exception of decreased IL-6 levels in the delayed-release group compared with levels that remained constant in the immediate-release prednisone group.19

**Safety Profile**

The results showed no clinically relevant differences in the safety profiles of the 2 treatment groups (Figure).19

In each group, 41% of the patients reported ≥1 adverse event. In approximately one third of all cases, these events were deemed treatment-related. The most frequent adverse event (AE) was a worsening of RA. Other events seen most frequently included upper abdominal pain, nasopharyngitis, headache, flushing, and nausea.19

The AE profile was consistent with the underlying disease, the patient population, and the known safety profiles of prednisone and concomitant treatments for RA.19

Discontinuations because of treatment-related AEs were reported in 8% of the delayed-release group and in 7% of the immediate-release group. The frequency of serious AEs was low—3% in the delayed-release prednisone group and 2% in the immediate-release prednisone group. Only 1 serious event was judged to be related to prednisone (ie, a depressed level of consciousness in the immediate-release group). One death was reported in the immediate-release group and was not considered related to study drug.19

**CAPRA-2**

**Trial Design**

CAPRA-2 was a 12-week, randomized, double-blind, parallel-group, placebo-controlled study that compared delayed-release prednisone (ie, Rayos) with placebo. After a 1-week screening period, 350 patients were randomized in a 2:1 ratio to receive delayed-release prednisone 5 mg daily or to placebo in the evening, with or after their evening meal in addition to their standard DMARD treatment.10

The primary end point was the percentage of patients who achieved a 20% improvement in RA signs and symptoms according to ACR criteria (ACR20) at the end of the 12-week treatment phase. Other end points were changes in morning pain, duration of morning stiffness, DAS28, and health-related quality of life (QOL).10

**Patient Population**

The study enrolled 350 patients (aged 18-80 years; mean age, 57 years) with a diagnosis of RA who had been taking DMARDs for at least 6 months. Other eligibility requirements included morning stiffness duration of at least 45 minutes on at least 4 of 7 days of screening, ≥4 swollen joints, and ≥4 tender joints. Baseline demographics were similar in the 2 treatment arms. Approximately 99% of the patients were taking DMARDs, and
approximately 72% were taking NSAIDs. At baseline, the 2 groups had comparable scores of pain and other RA-related symptoms, laboratory parameters, and health-related QOL.10

Efficacy
Clinical responses with delayed-release prednisone occurred rapidly, with most clinical end points favoring this medication over placebo. Differences in response between the 2 groups emerged as early as 2 weeks after the initiation of treatment, and responses were maintained for the remainder of the study.10

As illustrated in Table 1 and Table 2, the ACR20 response rate was 47% for delayed-release prednisone versus 29% for placebo (P <.001), and a 50% improvement in the signs and symptoms of RA, as shown by ACR50, was seen in 22% versus 10% of patients (P <.006), respectively.10,20

A greater reduction in morning stiffness was observed with delayed-release prednisone at week 12 than with the placebo: 55% versus 35% (P <.002), respectively. Treatment with delayed-release prednisone achieved significantly greater reductions in DAS28 (P <.001), reflecting severity of disease, and fatigue (P = .003) compared with placebo. A significantly greater improvement in physical function was seen with delayed-release prednisone versus placebo (P <.001) at week 12, as reflected by the SF-36 physical component score.10

Safety Profile
Delayed-release prednisone was generally well tolerated, with no life-threatening AEs or deaths reported during the trial. The incidence of AEs was similar for delayed-release prednisone (43%) and placebo (49%). The rate of treatment-related AEs was similar in the 2 groups: 7.8% for delayed-release prednisone versus 8.4% for placebo.10

The most frequent AEs in both groups were related to the worsening of RA and included arthralgia and aggravated RA; these events were seen more frequently with placebo than with delayed-release prednisone. The incidence of infection was similar in the 2 groups (13% vs 12%, respectively), as well as nasopharyngitis (approximately 4%), the most frequently reported type of infection.10

Serious AEs were reported in 1 patient (0.4%) in the delayed-release prednisone group versus 2 (1.7%) in the placebo group; none of these events were deemed severe or treatment-related. No clinically relevant changes in hematologic or biochemical parameters or vital signs were reported during the 12-week study.10

The study was not sufficiently long to assess any effects on structural damage and disease progression. Longer-term studies are needed to demonstrate safety and tolerability with prolonged treatment.10

Mechanism of Action of Rayos
Glucocorticoids represent a cornerstone of therapy for inflammatory-mediated diseases. Conventional prednisone is typically given in the morning upon awakening, when cortisol levels and symptoms are at their peak. Patients with RA have severe morning stiffness and pain upon awakening. Designing a drug delivery system for prednisone using the principles of chronotherapy has the goal of optimizing glucocorticoid therapy. By administering delayed-release prednisone at bedtime, the release of the active drug is delayed for approximately 4 hours; thereby, the drug is available to blunt the peak in cortisol, as well as inflammation-related symptoms.1

Dosing
For adults, the dosage of delayed-release prednisone should be individualized according to the severity of the RA and the patient’s response. These considerations should also be applied to children, rather than relying strictly on ratios for age or body weight.20

Rayos is a delayed-release formulation of prednisone, and the active substance is released approximately 4 hours after administration. The timing of administration should take into account the drug’s delayed-release pharmacokinetics, as well as the disease under treatment.20

Depending on the disease entity, the initial dose of delayed-release prednisone can range from 5 mg to 60 mg daily. For patients switching to delayed-release prednisone from another form of prednisone, an equipotent dose of Rayos should be used.20

Dose Modifications Based on Response
Lower doses of delayed-release prednisone should be sufficient for the treatment of less severe disease, whereas higher doses may initially be needed for selected patients with more severe disease. The initial dose should be maintained or adjusted until a satisfactory response is achieved. When the response to a trial of delayed-release prednisone is suboptimal, the drug should be stopped and the patient switched to another medication. It is important to individualize dosages of the drug according to the disease being treated and the patient’s response.20

Once a favorable response is achieved with delayed-release prednisone, the initial dose should be decreased in small decrements at timed intervals to determine the lowest dosage for maintaining an adequate response. Constant monitoring is required to ensure appropriate dosing.20

Dose Adjustment
Adjustments in dosage may be needed for changes in clinical status because of remission or disease exacerbation, the patient’s individual response, and effects of stress that are not disease-related. Treatment should be
stopped if spontaneous remissions occur. When delayed-release prednisone is discontinued, withdrawal should be gradual, not abrupt.20

Contraindications

Delayed-release prednisone is contraindicated in patients with known hypersensitivity to prednisone or any of the formulation’s inactive ingredients. Although anaphylaxis is rare, this event has been reported in patients taking corticosteroid therapy.20

Warnings and Precautions

Patients receiving chronic treatment with delayed-release prednisone should be monitored for hypothalamic-pituitary-adrenal axis suppression, a condition with the potential to produce corticosteroid insufficiency when treatment with delayed-release prednisone is withdrawn. Gradual withdrawal will minimize this risk.20

Patients taking this drug are at an increased risk of infection from many types of pathogens. Furthermore, corticosteroids such as delayed-release prednisone may mask signs of infection and increase vulnerability to new infections, as well as exacerbate existing infections and increase the risk of disseminated infections. Prophylaxis should be considered for patients exposed to chickenpox or measles while taking corticosteroids.20

Corticosteroids may increase the risk of reactivation or exacerbation of latent infection, including latent tuberculosis and latent amebiasis. Latent or active amebiasis should be excluded before initiating corticosteroid therapy if a patient has traveled to tropical countries or if the patient has diarrhea of unknown origin.20

Corticosteroids can alter blood pressure and the retention of salt and water, and they can increase the excretion of potassium and calcium. These agents should be used with caution in patients with congestive heart failure, hypertension, renal insufficiency, or recent myocardial infarction.20

Corticosteroids should also be used with caution in patients with signs of impending gastrointestinal perforation or other gastrointestinal infections or conditions. These agents can also exacerbate existing behavioral or mood disturbances, reduce bone density, and exert untoward ophthalmic effects with prolonged use.20

Intraocular pressure should be monitored in patients taking corticosteroids for longer than 6 weeks.20

Administration of live or attenuated vaccines is contraindicated in patients taking immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be given, but response is not assured. Patients taking corticosteroids should not receive vaccination against smallpox.20

Precautions in Special Populations

The long-term use of corticosteroids in children can slow growth and development.20 The use of corticosteroids during pregnancy is not recommended, because of the potential for birth defects and decreased birth weights.20

Conclusion

The FDA’s approval of delayed-release prednisone provides a new therapeutic option for patients with RA and with other inflammatory and rheumatic conditions, including polymyalgia rheumatica, psoriatic arthritis, ankylosing spondylitis, asthma, and COPD. This new agent offers an improved mechanism of action that facilitates the optimal release of prednisone very early in the morning, when disease symptoms peak, thereby promoting improved response rate in these patients. Using the oral formulation may also help patients better control their joint pain and inflammation, as well as other symptoms, and enhance their overall function and health-related QOL.

References