Glucocorticoids and Rheumatoid Arthritis

Joana Fonseca Ferreira, MD[a], Alaa Abdelkhalik Ahmed Mohamed, MD[b], Paul Emery, MA, MD, FRCP, FRCPE, FMedSci[c,*]

KEYWORDS

• Rheumatoid arthritis • Glucocorticoids • Prednisolone • Dose • Side effect
• Drug-drug interactions

KEY POINTS

- Endogenous glucocorticoids (GCs) are produced in the adrenal cortex.
- GCs exert their effect by genomic and nongenomic mechanisms.
- GCs improve pain, morning stiffness, and fatigue.
- In early rheumatoid arthritis (RA), low-dose to medium-dose GCs can prevent joint damage.
- In clinical practice, low doses of GCs can be used in RA as a maintenance therapy. Medium and high doses are used initially as a bridge therapy. Very high doses or pulse therapy are reserved for acute life-threatening or organ-threatening complications.

INTRODUCTION

Glucocorticoids (GCs) were discovered in the 1940s by Kendal and Hench and were administered for the first time to patients with rheumatoid arthritis (RA) in 1948. Two years later, Drs Kendal and Hench won the Nobel Prize.

This was the first time a medication had ever brought relief to patients with arthritis. However, in the following years, side effects were reported.[1]

In the last 7 decades, the mechanism of action has been elucidated. There are 2 fundamental modes of actions: genomic and nongenomic action. The genomic mechanism starts with diffusion of the free plasmatic hormone through the membrane lipids.

[a] Rheumatology Unit, Hospitais da Universidade de Coimbra, Centro Hospitalar e Universitário de Coimbra, Praceta Prof. Mota Pinto, 3000-075 Coimbra, Portugal; [b] Rheumatology, Physical medicine and Rehabilitation Department, Assiut University Hospitals, Assiut 71515, Egypt; [c] Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospital NHS Trust and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, Chapeltown Road, Leeds LS7 4SA, UK
* Corresponding author.
E-mail address: p.emery@leeds.ac.uk

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A binding site for the hormone is situated on cytoplasmic and nuclear receptors. The GC receptor (GCR) complex enters through nuclear pores and binds to the DNA, resulting in modification of gene transcription and messenger RNA production, and the subsequent translation and protein synthesis. The GCR complex also affects post-transcription events, resulting in alteration of cellular structure and activity, such as leukocytosis with neutrophil increase and reduction of all other leukocyte subsets.[2,3]

Nongenomic effects are complex; they occur more rapidly and involve membrane-bound receptors. This mechanism needs further clarification but it is hoped that doing so will lead to new therapeutic targets.[3]

CLINICAL APPLICATIONS IN RHEUMATOID ARTHRITIS

Inflammation Under Control

Administration of GCs results in diminished activation, proliferation, differentiation, and survival of various inflammatory cells.[4] The higher the dose, the stronger is the effect. In RA, low doses are effective; however, in life-threatening events, high doses are often used. Although, the absolute number of inflammatory cell subsets is decreased, the total blood leukocyte count increases. This increase could be explained by reduction of the adhesion molecules, which subsequently prevents migration of neutrophils from the circulation to the tissues and increases their levels in plasma. Leukocyte subsets all decrease except B cells, which remain stable. GCs inhibit T-helper 1 (Th1) cells, resulting in a reduction of proinflammatory cytokine levels, such as interleukin (IL)-1β, IL-2, IL-3, IL-6, tumor necrosis factor alpha, interferon gamma, and IL-17 and explaining their antiinflammatory effect.[2]

Pain Relief and Structural Progression

Relief of arthritis symptoms, including pain and swelling, is the predominant effect of GCs. New therapeutic strategies target rapid relief of symptoms but also aim to change the course of the disease (ie, preventing joint damage).[5] A high-quality Cochrane Review identified 15 studies with 1414 patients and confirmed that treatment with GCs provided not only symptom relief but also reduction of radiographic progression with low doses of GCs in patients with early arthritis (RA<2 years). All these studies chose low doses of GCs (<7.5 mg/day) to minimize side effects.[6]

This Cochrane Review provides support that GCs behave as disease-modifying antirheumatic drugs (DMARDs) and should be included as the first line of therapy in early arthritis.[6]

Fatigue, Anxiety, and Depression

Other debilitating RA symptoms are fatigue, anxiety, and depression. In contrast with pain and morning stiffness, which correlate with the presence of proinflammatory cytokines, the pathophysiology of these symptoms is unclear.[5]

An analysis of 388 patients with early arthritis suggested an association between morning stiffness and fatigue.[7] Both symptoms improved after taking GCs, underscoring a potential common pathway. Consistent with these results, modified-release prednisone treatment for 12 weeks significantly reduces fatigue scores compared with placebo circadian administration of prednisone in rheumatoid arthritis (CAPRA-2).[8]

Depression and anxiety are sometimes related to disease activity and pain; amelioration of the disease activity and pain improves these symptoms. However, GCs can also have a psychological side effect that paradoxically results in increased anxiety (**Table 1**).