

## Editorial

### Corticosteroids: a double-edged sword in clinical practice

Cortisone, a steroid hormone secreted from the adrenal cortex, with its synthetic derivatives, has been an important therapeutic agent since its discovery by the combined efforts of three Nobel laureate scientists, Edward Calvin Kendall, Tadeusz Reichstein, and Philip Showalter Hench in 1950.<sup>1</sup> It was first used as a therapeutic in Rheumatoid Arthritis and, from then on, its derivatives have been used under the common name 'steroid' in numerous areas of medicine for the last 22 years, including the successful use of dexamethasone and methylprednisolone in recent days, in the management of hypoxemic COVID-19 pneumonia patients.<sup>2,3</sup> But it has long been realized in medical practice that this is one of the frequently prescribed drugs that warrant most judicious prescribing to avoid its related hazards which, at times produce alarming consequences. Chemically, (CS) are 17-carbon and 4-steroid-ring hydrocarbons that exert physiological functions in maintaining carbohydrate, protein, and, fat metabolism, surviving in stress, anti-inflammatory response, immune-suppression, anti-proliferation, vasoconstriction, and others through genomic and non-genomic mechanisms.<sup>4</sup> CS have been one of the most frequently discussed and investigated drugs among clinicians and researchers for ages. Generations of this drug, suitable for different clinical use, with different pharmacological properties and different routes of administration-topical, oral, intravenous, intramuscular, inhalation, intra-articular, and, intra-lesional, have been invented and widely used in clinical practice so far and, thus have become important therapeutic agents in almost all fields of medicine.

Of their innumerable uses, CS are used as essential replacements in different adrenocortical insufficient conditions like Addison's disease, Sheehan's syndrome, post-adrenalectomy state, etc. They are used as emergency medications in conditions like anaphylaxis, severe acute asthma, acute flares of autoimmune diseases, toxic pulmonary edema,

and, cerebral edema. They are sometimes prescribed for long-term uses in chronic diseases like inflammatory bowel disease, interstitial lung disease, connective tissue diseases, Myasthenia Gravis, Graves' ophthalmopathy, and others. Nonetheless, they also show prophylactic benefits after organ transplantation to prevent rejection of the graft and, in preterm delivery to allow fetal lung maturation.<sup>1</sup>

As big as the list of therapeutic benefits of CS is, bigger than that is the list of their adverse effects. So it is a matter of great challenge for a clinician to gain therapeutic benefit from them, standing on the spur of speculated adverse events that follow. For example, their first and highest initial use was as an anti-inflammatory agent, which was later on minimized owing to the development of adverse effects. In a meta-analysis of 2555 patients, the incidence of steroid-induced neuropsychiatric adverse effects was found to be 5.7%.<sup>5</sup> In another cohort study on 7421 patients, Cox's proportional hazards showed a 17% increased hazard of hypertension with CS at doses above 7.5 mg.<sup>6</sup> The prevalence of hypertension, diabetes mellitus, and, iatrogenic Cushing syndrome with long-term CS use are, >30%, 30-40% and, 25-93% respectively.<sup>7,8</sup> Acute a vascular necrosis (AVN) of the femoral head can occur in 40% of steroid recipients. It can also occur in prolonged therapy situations presumably due to vascular impedance by mechanisms not fully understood. And CS-induced AVN is the commonest clinical condition requiring arthroplasty correction.<sup>9</sup> A lot more other adverse effects involving ophthalmic, gastrointestinal, endocrine, musculoskeletal, skin, hematologic, and immune systems of the body frequently develop with the use of systemic CS.<sup>10</sup>

Moreover, CS treatment can sometimes be associated with resistance to therapy due to receptor mutation and, receptor gene polymorphism. And discontinuation of medicine can cause a relapse of the treated illness, and more adversely, abrupt and/or rapid withdrawal

can lead to adrenal insufficiency due to prolonged suppression of the hypothalamic-pituitary axis.<sup>11</sup> In 30% of cases, anabolic-androgenic-steroid use causes dependence on the drug followed by self-administration despite realizing its side effects.<sup>12</sup> All these issues impose an intense sense of uncertainty and concern while prescribing CS for a specific indication in clinical practice.

### *A few case scenario*

**Case 1:** A 70-year-old diabetic woman gets 3 doses of monthly intramuscular shots of 40mg triamcinolone for osteoarthritis. She reports 2 months after the last injection with restlessness. She has a Cushingoid appearance but has serum hormone values suggestive of adrenal insufficiency as evidenced by morning and evening serum cortisol and baseline serum ACTH values of 8.45 ng/ml, 9.22 ng/ml, and 3.15 pg/ml, respectively, and short Synacthen test values of 43.32 ng/ml at 30 minutes and 79.41 ng/ml at 60 minutes, suggestive of steroid-induced adrenal insufficiency.

**Case 2:** A 60-year-old male farmer is diagnosed with a case of idiopathic diffuse parenchymal lung disease and is prescribed a 16mg daily dose of oral methylprednisolone. He gradually develops backaches and aches in his lower limbs two years after the prescription. He has difficulty rising from a seat. His bone mineral densitometry shows a z score of 3.5 in the spine and 3.1 in the femurs, suggestive of osteoporosis, most likely induced by prolonged CS therapy.

**Case 3:** A 34-year-old housewife is diagnosed with a case of systemic lupus erythematosus. She has been prescribed a daily dose of prednisolone 7.5 mg. She gradually develops pain in her right hip and buttock, which worsens with weight-bearing, after three years of uneventful therapy. An X-ray right hip reveals a crescent sign in the right femoral head suggestive of AVN.

It is a matter of great responsibility for the prescribers to use CS appropriately and cautiously. It is not an over-the-counter

medicine and should only be prescribed when indicated. Adverse effects should be considered and explained to recipients. Authentic withdrawal protocols should be followed to avoid adrenal insufficiency. And, patients should clearly and strongly be warned about the dangers of self-prescription. It should be kept in mind that the art of practicing medicine lies in remaining in the safe zone within the margins of therapeutic effects and side effects.

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