Infection Risk and Safety of Corticosteroid Use

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KEYWORDS

• Corticosteroids • Bacterial infections • Rheumatic diseases
• Opportunistic infections

KEY POINTS

- The risk of serious bacterial infections is higher in patients with rheumatic diseases who are taking corticosteroids.
- The risk of certain opportunistic infections (OIs), such as *Pneumocystis jiroveci* pneumonia (PJP), herpes zoster (HZ), and tuberculosis (TB), has also been shown higher.
- Vaccination and screening strategies should be used to decrease the risk for these and other infections in patients with rheumatic diseases who are starting corticosteroids.

INTRODUCTION

Because of their potent anti-inflammatory properties, corticosteroids have been used for decades to treat many diseases, including rheumatic diseases. They are frequently used in chronic fashion for rheumatoid arthritis (RA), and several randomized controlled trials (RCTs) have established their efficacy. They have been shown to reduce radiographic disease progression and improve disease activity.[1,2] The dosages used in RA are often lower than for other rheumatic diseases, such as vasculitis or systemic lupus erythematosus (SLE).[3]

Because of their known efficacy in RA, corticosteroids are likely to be used frequently as monotherapy or in combination with biologic or nonbiologic disease-modifying antirheumatic drugs (DMARDs), and it is important for clinicians to know the risks associated with this therapy. There are several well-established risks,

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including osteoporosis, avascular necrosis, glaucoma, diabetes mellitus, and cardiovascular disease.[4–9] Although an increased risk of infection is also well established, controversy remains regarding the dose and duration of corticosteroids necessary to substantially raise risk. In addition, there are questions regarding which specific types of infections have an increased risk. The prevention and surveillance for infection among patients with rheumatic diseases taking corticosteroids also vary widely and are often provider dependent.

There are multiple anti-inflammatory and immunosuppressive effects of glucocorticoids. They affect virtually all immune cells, and their precise effects depend on the differentiation and activation state of the cell.[10] They antagonize macrophage differentiation as well as suppress macrophage production of interleukin 1, interleukin 6, tumor necrosis factor, and the proinflammatory prostaglandins and leukotrienes. Glucocorticoids also suppress the tumoricidal and microbicidal activities of activated macrophages.[11] These agents also suppress neutrophil adhesion to endothelial cells and impair their lysosomal enzyme release, respiratory burst, and chemotaxis to the inflamed site.[11] Glucocorticoids can cause marked lymphopenia involving all lymphocyte subpopulations; they inhibit T-cell activation by inhibiting interleukins 2, 3, 4, and 6.[11] The maturity of double-positive T lymphocytes ($CD4^+$ $CD8^+$), which are the majority of the thymocyte population, can be impaired by glucocorticoids because these cells are highly sensitive to glucocorticoid induced apoptosis.[12] Glucocorticoids also have immunosuppressive effects on maturation and function of dendritic cells (antigen-presenting cells that can interact with naïve T cells to instruct the adaptive immune response).[12,13]

INFECTION IN RHEUMATIC DISEASES AND CORTICOSTEROIDS

At baseline, patients with rheumatic diseases have an increased risk of infection over the general population, and this has been particularly well documented in RA. Smitten and colleagues[14] evaluated 24,530 patients with RA from the PharMetrics claims database in the United States and 500,000 non-RA controls. They documented age-adjusted and gender-adjusted incidence of hospitalized infections of 4.4 and 2.2 per 100 person-years in RA and non-RA cohorts, respectively. A population-based study in Minnesota identified hospitalized infection incidence of 9 of 100 person-years among patients with RA compared with 5 of 100 in those without RA. After controlling for age, gender, smoking, corticosteroid use, and other factors, they found that patients with RA still had a higher risk of infection (hazard ratio [HR] 1.83; 95% CI, 1.52–2.21).[15] This increased infection risk is likely multifactorial and in part due to the immunodysregulation and mechanical joint/organ damage associated with the disease.[15,16] Other rheumatic diseases, such as SLE, are also well documented as having higher infection rates likely in part due to impaired cellular and humoral immunity.[17–19]

The current evidence base detailing the risk of infections with corticosteroids is largely derived from RCTs and observational studies (both population-based and single/multicenter). In general, individual RCTs have reported few infections. Observational studies, however, have consistently shown increased risks with corticosteroids. In general, most of these studies have divided daily prednisone dosages into low-dose, moderate-dose, and high-dose categories. Although this is somewhat arbitrary, most studies consider low-dose therapy as less than 5 mg daily, or by some studies less than or equal to 7.5 mg, of prednisone or equivalent daily. The duration of therapy is also important but perhaps is less well defined in terms of associated infectious risk. The exact doses and duration that substantially change the benefit-risk equation for corticosteroids likely vary by individual and underlying risk factors for infection.