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Long-Term Steroid-Based Therapy: Risk of Infectious Complications in Immunosuppressed Kidney-Transplant Recipients as Compared to the General Population

Malvezzi P[1], Jouve T[1,2,3] and Rostaing L[1,2,3]*

[1]Service de Néphrologie, Hémodialyse, Aphérèses, et Transplantation, CHU Grenoble-Alpes, France

[2]Université Grenoble-Alpes, Grenoble, France

[3]INSERM U563, IFR–BMT, CHU Purpan, Toulouse, France

Mini Review

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***Corresponding author:** Lionel Rostaing, Service de Clinique Universitaire de Néphrologie, Hémodialyse, Aphérèses, et Transplantation, Avenue Maquis du Grésivaudan, 38700 La Tronche, France, Tel: +33476768945; Email: LRostaing@chu-grenoble.fr

Abstract

Steroids are used to treat chronic inflammatory diseases and are often given as part of an immunosuppressive therapy to prevent acute/chronic kidney-graft rejection. However, steroids have many side-effects and may increase the risk of infectious complications. This review reports on the infectious complications that occur in those within the general population that receive chronic steroid therapy compared to kidney-transplant recipients that receive steroids as part of their immunosuppressive regimen. Many studies show that patients with rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, or inflammatory bowel disease, and treated for >90 days with a steroid-based therapy, have a significantly greater likelihood of developing a serious infectious complication. However, kidney-transplant recipients that receive long-term steroid therapy, when compared to those with steroid-free immuno suppression, have the same risk of developing an infectious complication: this may be because the current immunosuppressive drugs, such calcineurin inhibitors and mycophenolic acid, are so powerful that they offset the risks linked to steroids.

Keywords: Glucocorticoid; Infections; Kidney transplantation; Sepsis; Pulmonary infection

Introduction

In 1933, several hormones were isolated from animal adrenal glands, amongst them was cortisol. In 1949, Hench et al. published their findings on the effects of this hormone (17-hydroxy-11-dehydrocorticosterone: compound E) and the pituitary adrenocortical hormone on rheumatoid arthritis (RA) [1]. It was clear from this study that cortisone could change the fate of RA [2].

Natural glucocorticoids, e.g. hydrocortisone, are used as a substitutive therapy in adrenal deficiency. Synthetic glucocorticoids are much powerful than natural hormones, i.e. their anti-inflammatory potency is increased and they have very little effect as a mineralocorticoid.

There are short-acting steroids, such as prednisone, prednisolone and methyl prednisolone; their anti-inflammatory power is 4–5 times greater than natural cortisol. Intermediate-action steroids, such as triamcinolone and paramethasone, have anti-inflammatory powers that are 5–10 greater than natural cortisol. The anti-inflammatory power of long-acting steroids, such as betamethasone, dexamethasone and cortivazol, is 25–30 greater (and up to 60 times greater for cortivazol). However, steroid use was initially limited because of the significant side-effects, such as mental disturbance, which can occur with cortisone and ACTH, and many other adverse effects, including metabolic disorders, endocrinal disturbances, digestive symptoms (including bleeding from stress ulcers), and infectious complications [3,4].

In a recent meta-analysis that included 28 studies (2382 patients), the overall risk of adverse events was 150 per 100 patient-years (95% confidence interval [CI]: 132–169). Psychological and behavioural adverse events (e.g. minor mood disturbances) were most frequently reported, followed by gastrointestinal events (e.g. dyspepsia, dysphagia). Infectious complications included bacterial infections, reactivation of tuberculosis or toxoplasmosis and viral infections, including herpes zoster virus and reactivation of viral hepatitis [5,6].

In a study based on the National Health and Nutrition Examination Survey (NHANES), conducted between 1999 and 2005, the prevalence of glucocorticoid use in the US general population was 1.2% (95%CI: 1.1–1.4) after long-term use (mean >1,600 days) and infrequent use of anti-osteoporotic medications [7]. In an observational UK study, in the general population, over the past 20 years the long-term use of glucocorticoids (>3 months) has been 0.75% (95%CI: 0.74–0.75); **h**owever, this rose from 0.59% in 1989 to 0.79% in 2008. Long-term corticosteroid prescriptions for RA in the UK have significantly increased from 10.3 to 13.6%, and for polymyalgia rheumatica/giant cell arteritis they have increased from 57.6 to 66.5%. However, the numbers of prescriptions have decreased for asthma, chronic obstructive pulmonary disease and Crohn's disease. Although the number of prescriptions has remained stable for ulcerative colitis, when only incident cases were considered, the authors found a decrease in corticosteroid prescriptions for patients with RA and ulcerative colitis [8].

In addition to patients with chronic disease and that take glucocorticoids on a long-term basis, we need to consider patients with a solid-organ transplant (SOT), who number >1 million worldwide, with 117,733 new cases in 2013 (www.transplant-observatory.org). At least 50% of SOT patients take 5–10 mg of glucocorticoids per day over the long term.

In France, prednisone was approved in 1955, and is now registered to treat more than 100 diseases. We do not have national data for the prevalence of French patients taking glucocorticoids for a chronic disease for >3 months. However, assuming that the prevalence is similar to the UK or USA, an estimated 660,000 patients visit an estimated 58,104 general practitioners to receive glucocorticoids. Thus, a primary-care practitioner follows up, on average, 11 patients treated with glucocorticoids. With this in mind, it is of utmost importance that these patients are managed in the best way possible with regards to the side effects from glucocorticoids, particularly regarding infectious complications.

What is the Magnitude of Infectious Complications?

The General Population

A report written in 1989 pooled data from 71 randomized controlled clinical trials that compared steroids versus no steroids: the overall rate of infectious complications was greater for those receiving steroids, i.e. it increased by 60% (95%CI: 30–90%). However, this rate was not increased in those receiving a daily dose of <10 mg or a cumulative dose of <700 mg of prednisone (6). More recently, a study examined the risk of non-serious infections in older RA patients from Québec (*n*=16,207) and receiving chronic systemic glucocorticoids: the incidence of a non-serious infectious complication was 47.5/100 person-years, with an increased adjusted risk ratio of 20% (95%CI: 15–25%); in addition, a dose–response effect was evident [9].

Another study from Ontario (Canada) that included 86,039 senior RA patients, found serious infections occurred in 46.4 per 1,000 person-years. The most frequent events were respiratory infections, herpes zoster and skin/soft tissue infections [10]. In addition, the drug category associated with the greatest rate of infections was glucocorticoids, which exhibited clear dose–response relationship and had an Odds ratio ranging from 4.0 at low doses to 7.6 at high doses [10]. Still in Québec, Dixon et al. investigated the impact of oral glucocorticoid therapy on the risk of serious infection in the setting of older RA patients that had previously or were currently

receiving glucocorticoids: they found that current doses were associated with the greatest risk of infection. However, doses taken up to 2.5 years previously were also associated with increased risk, albeit to a lesser extent. For example, the current use of 5 mg prednisolone/day had a 30%, 46% or 100% increased risk of serious infections when used continuously for the last 3 months, 6 months, or 3 years, respectively [11].

Moreover, in a very large study that pooled RA patients from the US and the UK, it was shown that RA patients, as compared to non-RA patients, had an increased risk of herpes zoster (adjusted hazard ratio of 1.91;95%CI: 1.80–2.03), and that this greater risk was regardless of other concurrent therapies [12].

Similarly, patients with asthma and receiving inhaled corticosteroids within the previous 90 days were at increased risk for pneumonia or lower respiratory infections(2.04;95%CI: 1.59–2.64), with those receiving higher doses (≥1,000 μg) being at greatest risk [13]. Likewise, patients with chronic obstructive pulmonary disease and taking inhaled corticosteroids for more than 6 months (vs. a non-steroidal inhaled therapy) had a 34% increased risk of pneumonia, although this had no impact on 1-year all-cause mortality [14]. Finally, the chronic use of inhaled corticosteroids in a high-risk population of individuals who survived an episode of pneumonia was associated, in a5-year follow-up, with a 90% relative increased risk of recurrent pneumonia [15].

For patients with inflammatory bowel disease, a meta-analyses has shown an increased risk of all postoperative complications (OR 1.41, 95%CI: 1.07–1.87), as well as an increased risk of postoperative infectious complications (OR 1.68, 95%CI: 1.24–2.28) among patients receiving steroidal therapy. In addition, patients who received higher doses of perioperative oral steroids (>40 mg) had a higher risk of total complications (OR 2.04; 95%CI: 1.28–3.26) [16].

More recently, Fardet, et al. reported on a study that examined common infections in UK patients prescribed systemic glucocorticoids in primary-care facilities [17]. When compared to patients with the same condition but not exposed to glucocorticoids, the hazard ratios of infection in the glucocorticoid-exposed population (*n*=275,072 adults prescribed glucocorticoids orally for ≥15 days, 57.8% women, median age 63 years) ranged from 2.01 (1.83--2.19; $p<0.001$) for cutaneous cellulite is to 5.84 (5.61--6.08; $p<0.001$) for lower respiratory-tract infection. Conversely, there was no difference in the incidence of scabies, dermatophytosis and varicella. The relative increased risk was stable over the duration of exposure, except for lower respiratory-tract infections (LRTI) and candidiasis, which were much higher during the first weeks of exposure. This has huge implications for patients that have asthma or COPD and implies a closer follow-up is needed while these patients receive steroidal therapy and that they receive the appropriate vaccinations (influenza, pneumococcus). Secondly, when prescribing oral glucocorticoids, the physician needs to carefully examine the skin and mucosa in order monitor for mycosis (foot) or candidiasis (mouth).

Kidney-Transplant Patients

Patients with a solid-organ transplant may receive high-dose boluses of methyl-prednisolone (1g or 10mg/kg) to counter cellular acute-rejection episodes. Prednisolone therapy is more likely within the first phases of post-transplantation, and can be thereafter reduced to low-maintenance doses or even completely withdrawn when graft function is perfect. In addition, organ-transplant patients are also generally treated with other immunosuppressive drugs that target T-cell immunity; thus, the risk of infection is not solely related to glucocorticoids.

In the early years of transplantation (in the 1980s), in the absence of calcineurin inhibitors (cyclosporine and tacrolimus), patients were treated essentially with high-dose glucocorticoids plus azathioprine for prolonged periods of time. A few reports have correlated glucocorticoid dose with the risk of infection [18-19]. Patients treated over long periods of time with doses of >1mg/kg per day were subject to more viral infections, such as CMV and HSV, but also aspergillosis and tuberculosis [20-21].

In transplant medicine, these high-dose long-term treatments have been gradually abandoned, especially as new immunosuppressive drugs have become available. They have been replaced by short-duration pulses of corticosteroids, followed by very low-doses of steroids. This strategy is better tolerated by patients and causes fewer short- and long-term side effects. The mechanism(s) underlying this phenomenon is not well understood, but is probably due to the effect provoked by the massive dose and diffusion of drugs at cytosolic level [22].

Overall, in solid-organ transplantation, the learning curve has permitted integration of pulse therapy with

very low maintenance steroidal therapy, resulting in a very low risk of infection. This has been shown extensively in clinical trials, especially in those focusing on kidney transplantation where steroid avoidance or sparing has been compared to steroid maintenance [23,24]. Finally, Pascual, et al. reviewed available data in a very complete meta-analysis that included 30 studies and 5949 participants: the results are quite reassuring because there was no evidence of there being significantly more infections in patients that remained on steroids over longer periods [25]. This was true, even when steroid avoidance was compared to maintenance therapy, and probably reflects the strength of the other immunosuppressive drugs associated with steroids, which ultimately mask any eventual steroid pathogenicity. This meta-analyses has been recently updated, and its results confirm those from the 2009s [26]. It now includes 48 studies that involve 7803 randomised participants. There was no significant difference in the patients' mortality, either in studies that compared steroid withdrawal versus steroid maintenance (death at one year post-transplantation: RR 0.68, 95% CI 0.36--1.30) or in studies that compared steroid avoidance versus steroid maintenance (death at one year post-transplantation: RR 0.96, 95% CI 0.52-1.80). Similarly no significant difference in graft loss was found when steroid withdrawal was compared with steroid maintenance (i.e. graft loss excluding death with a functioning graft at one year post-transplantation: RR 1.17, 95% CI 0.72--1.92) and when steroid avoidance was compared with steroid maintenance (graft loss excluding death with a functioning graft at one year post-transplantation: RR 1.09, 95% CI 0.64--1.86). There was also no evidence to suggest a difference in harmful events, such as infection and malignancy, in adult kidney-transplant recipients.

Conclusion

The risk of infectious complications is not increased in kidney-transplant recipients that receive long-term low-dose steroids therapy compared to graft-recipients that do not receive steroids. This may be because steroids have a marginal impact compared to the other far many powerful immunosuppressive drugs given, i.e. calcineurin inhibitors and/or mycophenolic acid. Conversely, in the general population long-term steroid therapy significantly increases the risk of infectious complications.

References

1. Hench PS, Kendall EC, Slocumb CH, Polley HF (1949) The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and of pituitary adrenocortical hormone in arthritis: preliminary report. Ann Rheum Dis 8(2): 97-104.

2. Pickering GW (1950) Significance of the discovery of the effects of cortisone on rheumatoid arthritis. Lancet 2(6620): 81-84.

3. Clark LD, Bauer W, Cobb S (1952) Preliminary observations on mental disturbances occurring in patients under therapy cortisone and ACTH. N Engl J Med 246(6): 205-216.

4. Hoes JN, Jacobs JW, Verstappen SM, Bijlsma JW, Van der Heijden GJ (2000) Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. Ann Rheum Dis 68(12): 1833-1838.

5. Kass EH, Finland M (1958) Corticosteroids and infections. Adv Intern Med 9: 45-80.

6. Stuck A, Minder CE, Frey FJ (1989) Risk of infectious complications in patients taking glucocorticoids. Clin Infect Dis 11(6): 954-963.

7. Overman RA, Yeh JY, Deal CL (2013) Prevalence of oral glucocorticoid usage in the United States: a general population perspective. Arthritis Care Res 65: 294-298.

8. Fardet L, Petersen I, Nazareth I (2011) Prevalence of long-term oral glucocorticoid prescriptions in the UK over the past 20 years. Rheumatology 50: 1982-1990.

9. Dixon WG, Kezouh A, Bernatsky S, Suissa S (2011) The influence of systemic glucocorticoid therapy upon the risk of non-serious infection in older patients with rheumatoid arthritis: a nested case-control study. Ann Rheum Dis 70(6): 956-960.

10. Widdifield J, Bernatsky S, Paterson JM, Nadia Gunraj, J Carter Thorne, et al. (2013) Serious infections in a population-based cohort of 86,039 seniors with rheumatoid arthritis. Arthritis Care Res 65(3): 353-361.

11. Dixon WG, Abrahamowicz, Beauchamp ME, Ray DW, Bernatsky S, et al. (2012) Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. Ann Rheum Dis 71(7): 1128-1133.

12. Smitten AL, Choi HK, Hochberg MC, Suissa S, Simon TA, et al. (2007) The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. Arthritis Rheum 57(8): 1431-1438.

13. McKeever T, Harrison TW, Hubbard R, Shaw D (2013) Inhaled corticosteroids and the risk of pneumonia in people with asthma: a case-control study. Chest 144(6): 1788-1794.

14. Drummond MB, Dasenbrook EC, Pitz MW, Murphy DJ, Fan E (2008) Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA 300(20): 2407-2416.

15. Eurich DT, Lee C, Marrie TJ, Majumdar SR (2013) Inhaled corticosteroids and risk ofrecurrent pneumonia: a population-based, nested case-control study. Clin Infect Dis 57(8):1138-1144.

16. Subramanian V, Saxena S, Kang JY, Pollok RC (2008) Preoperative steroid use and risk of postoperative complications in patients with inflammatory bowel disease undergoing abdominal surgery. Am J Gastroenterol 103(9): 2373-2381.

17. Fardet L, Petersen I, Nazareth I (2016) Common Infections in Patients Prescribed Systemic Glucocorticoids in Primary Care: A Population-Based Cohort Study. PLoS Med 13(5): e1002024.

18. Papadakis J, Brown CB, Cameron JS, Adu D, Bewick M, et al. (1983) High versus "low" dose corticosteroids in recipients of cadaveric kidneys: prospective controlled trial. Br Med J Clin Res 286(6371): 1097-1100.

19. d'Apice AJ, Becker GJ, Kincaid-Smith P, Mathew TH, Ng J, et al. (1984) A prospective randomized trial of low-dose versus high-dose steroids in cadaveric renal transplantation. Transplantation 37: 373-377.

20. Gustafson TL, Schaffner W, Lavely GB, Stratton CW, Johnson HK, et al. (1983) Invasive aspergillosis in renal transplant recipients: correlation with corticosteroid therapy. J Infect Dis 148: 230-238.

21. Sahn SA, Lakshminarayan S (1976) Tuberculosis after corticosteroid therapy. Br J Dis Chest 70: 195-205.

22. Stahn C, Löwenberg M, Hommes DW, Buttgereit F (2007) Molecular mechanisms of glucocorticoid action and selective glucocorticoid receptor agonists. Mol Cell Endocrinol 275(1-2): 71-78.

23. Woodle ES, First MR, Pirsch J, Shihab F, Gaber AO, et al. (2008) A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. Ann Surg 248(4): 564-577.

24. Woodle ES, Peddi VR, Tomlanovich S, Mulgaonkar S, Kuo PC, et al. (2010) A prospective, randomized, multicenter study evaluating early corticosteroid withdrawal with Thymoglobulin in living-donor kidney transplantation.Clin Transplant 24(1): 73-83.

25. Pascual J, Zamora J, Galeano C, Royuela A, Quereda C (2009) Steroid avoidance or withdrawal for kidney transplant recipients. Cochrane Database Syst Rev 22(8): CD005632.

26. Haller MC, Royuela A, Nagler EV, Pascual J, Webster AC (2016) Steroid avoidance or withdrawal for kidney transplant recipients. Cochrane Database Syst Rev 22(8): CD005632.