HHS Public Access

Author manuscript

Rheum Dis Clin North Am. Author manuscript; available in PMC 2017 February 01.

Published in final edited form as:

Rheum Dis Clin North Am. 2016 February ; 42(1): 157–176. doi:10.1016/j.rdc.2015.08.004.

Infection Risk and Safety of Corticosteroid Use

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Synopsis

Corticosteroids are frequently used to treat rheumatic diseases. Their use comes with a number of well-established risks including osteoporosis, avascular necrosis, glaucoma, and diabetes. The risk of infection is of utmost concern and is well-documented, although randomized controlled trials (RCTs) of short term and lower dose steroids have generally shown little or no increased risk. Observational studies from the "real world", however, have consistently shown dose-dependent increases in risk for serious infections as well as certain opportunistic infections (e.g. herpes zoster, tuberculosis, and PJP). In patients who begin chronic steroid therapy, vaccination and screening strategies should be utilized in an attempt to mitigate this risk.

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 a number of 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 utilized in RA are often lower than for other rheumatic diseases such as vasculitis or lupus (SLE), [3].

Because of their known efficacy in RA, corticosteroids are likely to be used frequently as monotherapy or in combination with biologic or non-biologic disease modifying anti-rheumatic drugs (DMARDs), and it is important for clinicians to know the risks associated with this therapy. There are a number of well-established risks including osteoporosis, avascular necrosis, glaucoma, diabetes mellitus, and cardiovascular disease [4–9]. While 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 varies widely, and is often provider dependent.

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Disclosures

JY has no financial disclosures. SAN has no financial disclosures. KLW has no relevant disclosures.

There are multiple anti-inflammatory and immunosuppressive effects of glucocorticoids. They affect virtually all immune cells, and their precise effects depend upon 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 pro-inflammatory 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, the 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 as these cells are highly sensitive to glucocorticoid induced apoptosis [12]. Glucocorticoids also have immunosuppressive effects on dendritic cell (antigen presenting cells that can interact with naïve T cells to instruct the adaptive immune response) maturation and function [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 et al [14]. evaluated 24,530 patients with RA from the PharMetrics claims database and 500,000 non-RA controls. They documented age and sex-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 9/100 person-years among patients with RA as compared to 5/100 in those without RA. After controlling for age, sex, 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% confidence interval (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 to have 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. However, observational studies have consistently shown increased risks with corticosteroids. In general, most of these studies have divided daily prednisone dosages into “low”, “moderate”, and “high” dose categories. While this is somewhat arbitrary, most studies consider “low” dose therapy as less than 5mg daily, or by some 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 dosages and duration that substantially change the benefit-risk equation for corticosteroids likely varies by the individual and their underlying risk factors for infection.

Randomized Controlled Trials (RCTs)

A number of trials evaluating the efficacy and/or safety of corticosteroids have been conducted in RA (Table 1). In most RCTs, the prednisone dose and the duration of therapy were clearly defined, however the low number of patients enrolled in the trials and the lack of a standardized way of reporting adverse events in these publications makes interpretation difficult. For example, few RCTs clearly reported the number of serious bacterial infections in each treatment arm. Dixon et al [20] recently performed a meta-analysis of RCTs published through January 2010. (Table 1). They included 21 RCTs of patients with RA or undifferentiated inflammatory polyarthritis, treated with corticosteroids in one arm and no corticosteroids in the other arm through January 2010. The prednisone dose varied between the trials, but was mostly less than 10 mg daily. A few trials included pulse doses of steroids and others included step-down prednisone regimens. The duration of treatment was relatively short compared with the observational studies, and did not exceed 3.5 years. No significant increased risk of infection was noted in the corticosteroid arms in most of the trials. Overall, they found 5.8% and 5.4% of the corticosteroid treated and non-corticosteroid treated groups had infections, respectively. There was no significant difference between the two groups, with a relative risk (RR) of infection associated with corticosteroid therapy of 0.97 (95% CI 0.69, 1.36). RCTs published since this meta-analysis are similar in both the dose of prednisone used and infections reported.

Observational studies

Observational studies have consistently demonstrated an increased risk of serious infections (generally defined as infections requiring hospitalization, intravenous (IV) antibiotics, or resulting in disability or death) sometimes even with prednisone equivalent (PEQ) doses of 5 mg or less daily. A national collaboration of observational databases (the Safety Assessment in Biologic Therapy [SABER]) in the United States found that in patients with RA systemic corticosteroid use was significantly associated with increased risk of serious bacterial infections, with a stepwise increase in risk of infection with higher steroid doses with an adjusted (a)HR of 1.32 (95% CI 1.10,1.58) for PEQ less than 5 mg/day, 1.78 (95% CI 1.47, 2.15) for 5–10 mg/day, and 2.95 (95% CI 2.41–3.61) for doses >10 mg/day [30]. Dixon et al [31]. performed a nested case-control analysis of 16,207 patients aged ≥ 65 years with RA in Quebec, Canada between 1985 and 2003. After adjusting for disease severity, other DMARDs, and co-morbidities, they found an increased risk of serious bacterial infections with as low as 5 mg PEQ for one week as well as a dose and duration dependent stepwise increase in the risk of serious bacterial infections. In this study the adjusted odds ratios (aOR) of serious bacterial infections were 1.03 (95% CI 1.02–1.11) and 2.0 (95% CI 1.69–2.26) in current users of 5 mg of prednisone daily for the past 7 days and 5 mg daily for the past 3 years, respectively.

Other studies too have reiterated the idea that even “low-dose” steroids may pose a hazard for patients. In another population-based study in patients with rheumatoid arthritis, Wolfe et al [32]. identified an increased risk for hospitalized pneumonia for prednisone dose 5 mg/day (HR 1.4 [95% CI 1.1, 1.6]) with a higher risk at doses greater than 10 mg daily [HR 2.3 (95% CI 1.6, 3.2)]. Smitten et al [14]. found that doses ≤5 mg daily were associated with

an increased risk of hospitalized infections (RR 1.32; 95% CI 1.06, 1.63). An analysis of Medicare beneficiaries with RA found that compared to methotrexate alone, glucocorticoid use doubled the rate of serious bacterial infections. This increased risk was dose-dependent with a RR of 1.53 (95% CI 0.95, 2.48) for doses between 6–9 mg up to 5.48 (95% CI 3.29, 9.11) for doses greater than or equal to 20 mg/day [33]. Among 86,039 patients with RA aged ≥ 66 years in Ontario, Canada the OR of serious bacterial infections was the highest for current exposure to corticosteroids compared with other DMARDs. For those using less than 5 mg daily, the OR was 3.96 (95% CI 3.67, 4.27) and for those using >20 mg/day it was 7.57 (95% CI 6.87, 8.34) [34].

On the other hand, other studies have found an increased risk only with higher doses of corticosteroids. In a retrospective analysis of 5,326 patients with RA, the risk of serious bacterial infection was only elevated in patients on a PEQ dose more than 10 mg daily with an (a)HR of 1.85 (95% CI 1.21–2.85), with no increased risk of infection at lower doses [35].

Dixon et al [20]. performed a meta-analysis of 42 observational studies [case control or cohort studies in patients with RA or inflammatory polyarthritis that reported a relative-risk (RR) or rate-ratio for the association between systemic corticosteroid therapy and infection]. The use of systemic corticosteroid therapy was associated with an increased risk of infection with a RR of 1.67 (95% CI 1.49, 1.87). There was a higher RR reported from case-control studies as compared to cohort studies with a RR of 1.95 (95% CI 1.61, 2.36) and 1.55 (95% CI 1.35, 1.79), respectively. Overall, no matter the study type, the risk of infection was found to be dose related: Studies with average PEQ < 5 mg/day had a RR of 1.37 (95% CI 1.18, 1.58), while studies with average PEQ 5–EQ 10 mg/day had RR of 1.93 (95% CI 1.67, 2.23), and only one study reported a RR for a PEQ dose of 10–20 mg/day [RR 2.97 (95% CI 1.89, 4.67)].

Lastly, work from Strangfeld et al. [36] suggested that for patients with RA the risk of serious infections decreased over time in biologic users because the use of biologic agents allowed for decreased prednisone utilization and/or dose over time (Table 2).

Opportunistic infections

In addition to serious bacterial infections, the risk of opportunistic infections (OIs) (infections generally thought to occur in those with “weakened” immune systems) is increased with corticosteroids. There is a well-documented risk with some infections such as *Pneumocystis jirovecci* pneumonia (PJP), herpes zoster (HZ), and tuberculosis (TB). The risk with other OIs such as aspergillosis, nontuberculous mycobacterial disease [41], candidiasis, and cryptococcosis has been suggested but the evidence base is less robust [42–44]. With some OIs such as TB and PJP that are endemic in certain parts of the world, the country being studied must be remembered when comparing incidence rates from different regions.

Pneumocystis jirovecci pneumonia (PJP)

The current evidence base regarding the association between PJP and corticosteroids is largely derived from case series and single center studies. A study from the Mayo Clinic of 116 patients with PJP (without HIV) from 1985–1991 found that 105 patients (91%) had received corticosteroids for a variety of indications within one month of PJP diagnosis, the median PEQ dose of patients with PJP was 30 mg/day [45]. A case-control study of 15 patients with SLE and PJP and 60 matched SLE patients without PJP revealed a high daily dose of prednisone (49 vs. 20 mg/day, $p<0.01$) to be associated with PJP infection [46]. In another case-series at Mayo, seven patients with giant cell arteritis (GCA) and PJP infection were identified. All were taking prednisone (median dose 50 mg (range 30–80 mg) daily) [47]. In an institutional case-series conducted within a Singapore hospital, the risk of developing PJP among patients with autoimmune disease was increased in those treated with high dose corticosteroids (≥ 30 mg/day oral prednisolone or equivalent) compared to those on a dose <30 mg/day oral prednisone (RR 19 [95% CI 2, 183]) [48].

There is increased colonization with PJP in patients with autoimmune disease on systemic corticosteroids [49]. In a prospective analysis, Fritzsche et al [50]. induced sputum in 102 patients with autoimmune disease on corticosteroids (for more than one week) and 117 healthy controls and performed PCR testing for PJP. In 29 (28.5%) patients with autoimmune disease and 3 (2.6%) healthy controls, they found evidence of PJP colonization (OR 15.10, [95% CI 4.43–51.38]). However, these patients were also on other DMARDs and the median prednisone dose did not differ between carriers and non-carriers. The significance of PJP colonization is unclear, although in those who develop disease, it is presumed colonization serves as the source of their disease.

Early observational studies in patients with anti-neutrophilic cytoplasmic antibodies (ANCA) associated vasculitis, notably granulomatosis with polyangiitis (GPA), showed that they are at an increased risk of PJP [51, 52].

Treatment with methotrexate, cyclophosphamide, and prednisone was associated with this risk [53–55]. In a study by Godeau et al [56]. a group of 12 patients with GPA and PJP was compared with 32 GPA patients without PJP by multivariate analysis. A low pretreatment lymphocyte count at a cut off of 800/mm3 ($p = 0.018$) and lymphocyte count at month 3 at a cut off of 600/mm3 were independently and significantly associated with PJP.

Herpes Zoster (HZ)

Several large population-based studies have found an association between corticosteroid use and herpes zoster (HZ) infection in those with rheumatic diseases, particularly RA. A study from Olmsted County, Minnesota using an inception cohort of 813 newly diagnosed RA patients between 1980 and 2007, and a similar group without RA, found the use of systemic steroids was significantly associated with HZ (HR 1.78 [95% CI 1.14, 2.76]) [57]. In another large population-based study, 10,614 RA patients and 1,721 patients with non-inflammatory musculoskeletal diseases (MSK) (osteoarthritis, mechanical back pain, etc.) without prior HZ were followed for 33,825 patient-years. The annualized incidence rate per 1000 patient-years was 13.2 in RA and 14.6 in MSK disease patients and did not differ significantly after

adjustment for age and sex. Prednisone use was found to be significantly associated with HZ in patients with RA, HR 1.5 (95% CI 1.2, 1.8). There was no difference between doses less than 5 mg and doses higher than 5 mg daily [58].

Other studies have evaluated the relationship between corticosteroid dose and incidence of HZ. In the German biologics registry 'Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) [59], risk factors for HZ episodes following the initiation of TNF inhibitors or conventional DMARDs were evaluated in 5040 patients. After adjusting for age and disease severity score, treatment with systemic corticosteroids of 10 mg daily or more was associated with an increased risk of HZ (aHR 2.52 [95% CI 1.12, 5.65]). No increased risk was noted with lower corticosteroid dose of 1–9 mg daily. In the SABER collaboration, a baseline use of 10 mg/day or more was associated with an increased risk of HZ among rheumatic disease patients compared to no baseline steroid use (aHR 2.13 [95% CI 1.64, 2.75]) [60]. In the CORRONA registry, a prednisone dose of at least 7.5 mg/day was associated with increased risk of HZ among RA patients (HR 1.78 [95% CI 1.20, 2.63]) compared to no glucocorticoid use [61].

In addition, in diseases other than RA such as psoriasis and dermatomyositis, the risk of HZ has also been shown to be increased with the use of corticosteroids. [62, 63].

Strongyloidiasis

Strongyloidiasis is a chronic parasitic infection, usually acquired through direct contact with contaminated soil. An estimated 30–100 million people are infected worldwide and the prevalence is higher in tropical and subtropical regions. Immunosuppressed patients might be at risk for hyperinfection syndrome and disseminated strongyloidiasis which has a high mortality rate, however there is no population based study to evaluate this risk.

Dora Buonfrate et al [64]. conducted a systematic review of case reports/case series published from January 1991 to April 2011 in the general population. They found 213 papers with a total of 244 cases. In the areas of low/no endemicity, approximately half of the patients were immigrants and 3% were veterans. Sixty seven percent of all cases were on corticosteroid treatment, and of those patients, 5.5% were being treated for lupus, 2.4% for RA, and 1.2 % for sarcoidosis. The mortality rate was high 153/244 (62.7%).

Tuberculosis

The baseline rate of TB is increased in those with rheumatic diseases compared to the general population. In Canada, the incidence rate of TB in patients with RA was 45.8/100,000 person-years compared to a baseline rate of 4.2/100,000 in the general population [65]. In a US cohort identified using an integrated claims database, the incidence rate of TB in the RA population was 21.33/100,000 compared to 9.48/100,000 in age and sex matched controls without RA [14]. A study out of the US using data from Kaiser Permanente Northern California (large health maintenance organization) found the rate of TB in the RA population was 8.7/100,000 compared to 2.8/100,000 in the general population and 5.2/100,000 in the general population 50 years and older [66]. This incidence rate varies according to the baseline rate in the population being studied. For example,

among patients with SLE in Hong Kong, the rate of TB was 700/100,000 compared to 110/100,000 in the general population [67]. A record linkage study in the United Kingdom found a relative risk (RR) of 9.4 (95% CI 7.9, 11.1) in those patients with SLE and 8.0 (95% CI 4.9, 12.2) in polymyositis for developing tuberculosis [68].

The increased risk for TB within these disease states is presumably due to both the diseases and the immunosuppressive therapies used to treat them, although surprisingly few observational studies have evaluated the risk of TB with corticosteroid use. A retrospective case control study in the United Kingdom (not limited to those with rheumatic diseases) found among 497 new cases of tuberculosis and 1,966 age and sex-matched controls that the adjusted odds ratio (aOR) for TB was 2.8 (95% CI 1.0, 7.9) for PEQ doses less than 15 mg/day and 7.7 (95% CI 2.8, 21.4) for doses greater than 15 mg/day [69]. Among 269 patients with rheumatic diseases treated for 1,035 corticosteroid years of therapy, the incidence rate of TB was 2,000/100,000, and they identified cumulative and mean daily steroid doses, or history of steroid pulse therapy as risk factors [70]. Among a cohort of 24,282 patients with RA in Quebec, 18% of those with tuberculosis were current glucocorticoid users compared to 8% for controls (p=0.03). The RR of TB was 2.4 (95% CI 1.1, 5.4) with use of corticosteroids [71]. Tam et al [67]. found the cumulative dose of prednisone and the presence of nephritis were independent risk factors for developing tuberculosis, and that patients with TB were more likely to have received intravenous pulse dose methylprednisolone. Increasing the prednisolone dose by one gram was associated with a 23% increased risk of developing TB.

Vaccination and Other Prevention Strategies

PJP

The dose and duration of prednisone use necessary to trigger PJP prophylaxis has not been rigorously established. The current practice of starting PJP prophylaxis in patients with PEQ doses of > 16 mg daily for more than 8 weeks is largely based on the aforementioned study from the Mayo Clinic in 1996 that included patients with a confirmed diagnosis of PJP between 1985 and 1991 (HIV negative). Ninety percent had used systemic corticosteroids in the month preceding infection. The median PEQ dose of patients with PJP was 30 mg/day, and the median duration of treatment prior to development of PJP was 12 weeks. Twenty-five percent of these patients were receiving as little as 16 mg of PEQ and 25% developed PJP in 8 weeks or less. However, the major limitations of this study are: the inability to calculate the absolute risk and the number needed to be treated, and also the relatively small number of patients with rheumatic diseases who were enrolled in the study. Only 22.4% of patients enrolled in this study had inflammatory diseases, while the remainder had hematologic malignancies, organ transplants, and/or miscellaneous conditions that were not classified [45].

Katsuyama et al [72] evaluated 702 patients with RA on biologic therapies. Nine patients (1.28%) developed PJP; eight of them (88.9%) were on corticosteroids at a mean dose (±SD) of 8.83 mg ± 14.9 mg. In the first phase of the study, they identified three risk factors for developing PCP: age ≥ 65 years, co-existence of pulmonary disease, and corticosteroids. In the second phase of the study, they enrolled 214 patients with RA who were also on

biologic therapy. They started 94 patients with at least 2 risk factors on prophylaxis with trimethoprim/sulfamethoxazole (TMP/SMX) or inhaled aerosolized pentamidine. Forty nine (22.9%) of the 214 study subjects were taking glucocorticoids with a mean dose of 6.28 mg +/− 6.46 mg prednisolone equivalent. There were no cases of PJP in the second phase of the study. They calculated that the incidence of PJP decreased from 0.93/100 patient-years in the first phase of the study to 0/100 patient years in the second phase of the study.

EULAR based recommendations encourage prophylaxis against *Pneumocystis jirovecii* with trimethoprim-sulphamethoxazole (TMP-SMX) in all patients with ANCA associated vasculitis being treated with cyclophosphamide [73]. There are multiple reports of PJP developing in patients treated with rituximab for hematological malignancies, solid organ transplantation, and autoimmune diseases [52, 55]. Therefore, there is also a suggestion for prophylaxis in patients with ANCA associated vasculitis who are treated with rituximab [52, 55]. There is no clear recommendation regarding duration of treatment, or if this treatment should be discontinued after induction therapy once maintenance treatment is introduced.

TMP-SMX should be prescribed as prophylaxis for either daily intake of one single strength tablet (80 mg trimethoprim and 400 mg sulfamethoxazole) or one double strength tablet three times weekly; with dose reduction in case of chronic kidney disease (one tablet three times weekly when glomerular filtration rate is 15– 30 mL/min) [52]. For patients who exhibit either intolerance or contraindication (i.e. glomerular filtration rate below 15 mL/min) to TMP-SMX, alternative therapy with atovaquone, 1500 mg daily, dapsone 100 mg daily, or once monthly 300 mg of nebulized pentamidine can be pursued [52].

In patients on methotrexate, TMP-SMX can increase the toxicity of methotrexate and should be used with caution [74]. Other strategies such as atovaquone, dapsone, or pentamidine may be considered in these cases as interactions with TMP-SMX could result in fatality [52].

HZ

The Centers for Disease Prevention and Control (CDC) guidelines recommend a single dose of the shingles vaccine (Zostavax®) for all persons aged ≥ 60 years who have no contraindications, including persons who report a previous episode of zoster [75]. The efficacy of the shingles vaccine was evaluated in a double blind randomized placebo-controlled trial involving 38,546 healthy adults aged ≥ 60 years who had a history of varicella or at least 30 years of residence in the continental US. The vaccine reduced the risk for developing HZ by 51.3% and postherpetic neuralgia by 66.5% [76].

Further, the CDC recommends vaccination in immunocompetent patients ≥ 60 years in whom immunosuppressive treatments are anticipated or who have diseases that might lead to immunodeficiency. Such patients should receive 1 dose of the shingles vaccine at least 14 days before initiation of immunosuppressive therapy. A study of patients with various autoimmune diseases compared with two cohorts of patients, one with diabetes and the other one with healthy controls, showed that the age-specific rates of HZ for patients with RA or SLE ≥ 40 years of age were greater than the corresponding rates in healthy individuals > 60 years old [77]. Given these elevated rates at baseline and that the vaccine is licensed for use

in those aged 50 and older [78], we advocate administration of the vaccine in all patients with rheumatic diseases once they reach the age of 50 as long as no contraindications are present.

As per American College of Rheumatology (ACR) guidelines, the shingles vaccine is contraindicated in patients taking biologic agents [79]. Per CDC guidelines, high dose corticosteroids (>20 mg/day of PEQ) lasting two or more weeks, methotrexate (>0.4 mg/Kg/week), azathioprine (>3.0 mg/Kg/day), 6-mercaptopurine (>1.5 mg/Kg/day) or biologic DMARDs are contraindicated for shingles vaccine and vaccination should be deferred for at least 1 month after discontinuation of such therapy [80].

TB

Currently to our knowledge, no rheumatic disease guidelines explicitly recommend screening for latent TB prior to initiation of corticosteroids, although the CDC guidelines on latent TB recommend screening in those who may need long-term immunosuppression including long term prednisone use [81]. Given that studies have shown an increased risk for development of TB in those with rheumatic diseases in general, and further increased risk with moderate to high dose steroids, we recommend screening for latent TB prior to initiating chronic therapy with corticosteroids. The dose of prednisone (or PEQ) that would put someone at risk is not entirely clear. The CDC's latent TB guidelines speculate that the dose of prednisone (or PEQ) that might increase risk is 15 mg for 2–4 weeks as this dose has been shown to suppress tuberculin reactivity [81], although the work discussed above suggests increased risk for chronic use of lower doses [69].

Further, interpretation of tests for latent TB, either tuberculin skin tests (TST) or interferon gamma release assays (IGRAs) such as QuantiFERON or T-SPOT.TB, may be difficult in those already taking corticosteroids. In a study of 724 patients with rheumatic diseases from Korea, corticosteroid use was associated with discordant results between TST and QuantiFERON tests with an OR of 2.44 (95% CI 1.24, 4.82) [82]. In patients with SLE, the use of corticosteroids adversely affected the results of TSTs, while for the T-SPOT.TB it did not [83]. Similarly, Matulis et al [84]. found that corticosteroids did not significantly affect IGRAs and that a positive IGRA response was associated with increased number of prognostically relevant risk factors for latent TB. Vassilopoulos et al [85]. found that the T-SPOT.TB was more sensitive than the TST in patients taking prednisone. Calabrese et al [86]evaluated the rate of indeterminate QuantiFERON testing in those with chronic inflammatory diseases (CID) compared to the general hospital population, as well as a healthy reference group and found indeterminate results in 5.3%, 1.9%, and 1.5%, respectively. In addition, they found in those patients with CID, steroids significantly increased the likelihood of an indeterminate test [aRR 1.4 (95% CI 1.02, 2.0)]. The use of corticosteroids has been associated with decreased performance of both TST and IGRAs increasing the risk of false negative results in patients currently taking corticosteroids [87]. Based on the totality of data published in this setting, we would recommend using IGRAs for screening if patients are already taking corticosteroids. However, any interpretation (of either a TST or IGRA) must take into account a patient's *a priori* risk of TB, and the fact

that the predictive values of the tests are also influenced by the patient's level of immunosuppression (Table 3).

Conclusions

While RCTs of corticosteroid use in rheumatic diseases have not reported an increased risk of infection, observational studies have found a consistently elevated risk of infections (both serious and opportunistic). Given this, the risk-benefit ratio must be kept in mind whenever long-term steroid therapy is considered.

The current EULAR recommendation for the use of corticosteroids in RA patients is to use low dose steroids for a limited time period during initial therapy for RA. However, given the risks of such therapy, this should be individualized so that certain patients with existing risk factors for infection (e.g. elderly, diabetes, other co-morbidities) might avoid such therapy or use only in a limited fashion. Proper patient selection, vaccination, and screening can limit the infection risks and should therefore be pursued in any patient taking corticosteroid therapy.

Acknowledgments

Funding

SAN's work upon this manuscript was in part supported by a National Institutes of Health training grant [2T32HL083808-06].

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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 such as pneumocystis jiroveci pneumonia (PJP), herpes zoster, and tuberculosis has also been shown to be higher. Vaccination and screening strategies should be employed to decrease the risk for these and other infections in patients with rheumatic diseases who are starting corticosteroids.

Table 1

Recent RCTS in patients with RA treated with systemic corticosteroids, Adapted from Dixon WG, Suissa S, Hudson M. The association between systemic glucocorticoid therapy and the risk of infection in patients with rheumatoid arthritis: Systematic review and meta-analyses. Arthritis Res Ther. 2011 Aug 31;13(4):R139; with permission.

Author Year Country Duration	Population	Arms of study	Type of infection/outcome	Outcome (Percentage of Infections in Each Treatment Arm)
Capell [21] 2004 UK 2 Years	RA patients not on DMARDs n=167	**1** SSZ plus prednisone 7 mg **2** SSZ plus placebo	• Infections leading to discontinuation	• None reported
Choy [22] 2008 UK 2 Years	Early RA patients on MTX within 2 years of diagnosis n=467	**1** MTX **2** MTX plus cyclosporine **3** MTX plus step-down prednisolone **4** MTX plus cyclosporine and Prednisolone	• Serious infections • Respiratory tract infections	• 5.9%, 2.5%, 3.4%, and 1.7% serious infections in the four arms, respectively • 46.1%, 42.8%, 42.6%, and 47.4% respiratory tract infections in the four arms, respectively
Durez [23] 2007 Belgium 46 Weeks	Early RA patients n=44	**1** MTX **2** MTX plus 1 g IV methylprednisolone **3** MTX plus infliximab infusions at weeks 0, 2, 6; then every 8 weeks	• Serious infections • Non-serious infections	• No serious infections • 100%, 80%, and 80% non-serious infections in the 3 respective arms
Gerlag [24] 2004 The Netherlands 2 Weeks	RA patients on DMARDs n=21	**1** Prednisolone 60 mg week 1, prednisolone 40 mg week 2 **2** Placebo	• Adverse events	• 9% skin infections in the placebo arm
Kirwan [25] 2004 Belgium, Sweden, UK 12 Weeks	Patients with RA n=143	**1** Budesonide 3 mg **2** Budesonide 9 mg **3** Prednisolone 7.5 mg **4** Placebo	• Viral Infection • Respiratory Infection	• 10.8%, 2.7%, 0%, and 0% viral infections in the four respective arms • 18.9%, 11.1%, 15.3%, and 3.2% respiratory infections in the four respective arms
Sheldon [26] 2003 UK 4 Weeks	Patients with RA n=26	**1** Budesonide **2** Placebo with usual DMARDs	• Adverse events	• 7.1% influenza infections in the budesonide arm

Author Year Country Duration	Population	Arms of study	Type of infection/outcome	Outcome (Percentage of Infections in Each Treatment Arm)
				• 8.3% influenza infections in the placebo arm
Svensson [1] 2005 Sweden 2 Years	Early RA patients on DMARDs n=250	**1** DMARD plus prednisolone 7.5 mg **2** DMARD, no prednisolone	• Withdrawal due to adverse events	• 0.7% infections in the non-prednisolone arm (1 abscess) • No discontinuations due to infection in the prednisolone arm
Van Everdingen [27] 2002 The Netherlands 2 Years	Previously untreated patients with early RA n=81	**1** Prednisolone 10 mg **2** Placebo	• Infections treated with antibiotics	• 42.5% infections in the prednisolone arm • 53.6% infections in the placebo arm
Wassenberg [2] 2005 Germany, Austria, Switzerland 2 Years	Patients with RA of < 2 years duration n=192	**1** Prednisolone 5 mg plus DMARD therapy **2** Placebo plus DMARD therapy	• Adverse events	• 3.1% bronchitis infections and 1% influenza infections in the prednisolone arm • 3% influenza infections in the placebo arm
Buttgereit [28] 2013 Europe and USA 12 weeks	Patients with RA on DMARDs n= 350	**1** MR Prednisone plus DMARDs **2** Placebo plus DMARDs	• Incidence of infection, nasopharyngitis, and bronchitis	• Incidence of infection in the prednisone group 13% vs. 12% in the placebo • Incidence of pharyngitis 4.8% in the prednisone group vs. 3.4 % in the placebo • Incidence of bronchitis 1.3% in the Prednisone groups vs. 4.2 % in the placebo
Bakker [29] 2012 Netherlands 2 years	Patients with RA, DMARDs naïve n= 239	**1** MTX plus prednisone 10 mg daily **2** MTX plus placebo	Infections treated with antibiotics	• 0.8% infections in the prednisone group • No infections in the placebo group

DMARD, disease modifying anti-rheumatic drugs; MR, modified-release; MTX, Methotrexate; RA, rheumatoid arthritis; SSZ, sulfasalazine.

* Inclusion and exclusion criteria of the RCTs after 2010 were based on Dixon et al meta-analysis.

Rheum Dis Clin North Am. Author manuscript; available in PMC 2017 February 01.

Table 2

Recent observational studies evaluating risk of infections in patients with RA treated with systemic corticosteroids

Author **Year** **Country** **Duration** **Study type**	**Population**	**Prednisone or PEQ dose**	**Infections**	**Results**	**Risk Ratios±**
Wolfe [32] 2006 USA 2001–2004 Prospective	RA n=16,788	PEQ ≤5 PEQ 5–10 PEQ >10	Pneumonia requiring hospitalization	Increased risk of infection; dose dependent	HR of hospitalization for pneumonia: • Any PEQ, HR 1.7 (95% CI 1.5–2) • PEQ ≤5, HR 1.4 (95% CI 1.1–1.6) • PEQ 5–10, HR 2.1 (95% CI 1.7–2.7) • PEQ >10, HR 2.3 (95% CI 1.6–3.2)
R. Curtis [35] 2007 USA 5/1998 - 12/2003 Retrospective	Patients with RA n=2,393 on TNF n=2,933 on MTX	PEQ ≤5 PEQ 5–10 PEQ >10	Hospitalization with confirmed bacterial infection	Increased risk of infection in patients on PEQ>10mg daily	Adj HR of confirmed infections • PEQ ≤5, HR 1.49 (95% CI 0.82–2.72) • PEQ 5–10, HR 1.46 (95% CI 0.84–2.54) • PEQ >10, HR 1.85 (95% CI 1.21–2.85)
Franklin [37] 2007 NOAR 1990–1999 Prospective	Patients with Inflammatory Polyarthritis n=2,108	Ever use	SBI	Increase risk of SBI	RR of SBI in patient on CS • Univariate analysis RR 2.3 (95% CI1.6 to 3.5) • Multivariate analysis RR 2.2 (95% CI 1.5 to 3.4)
Schneeweiss [33] 2007 USA 1/1995–12/2003 Prospective	RA >65 years old n=15,597	PEQ ≤ 5 PEQ 6–9 PEQ 10–19 PEQ ≥20	SBI	Increased risk of infection; dose dependent	Adjusted rate ratio (ARR) of SBI as per PEQ: • PEQ ≤5 mg ARR 1.34 (95% CI 0.85–2.13) • PEQ 6–9, ARR 1.53 (95% CI 0.95–2.48) • PEQ 10–19, ARR 2.97 (95% CI 1.89–4.68) • PEQ ≥20, ARR 5.48 (95% CI 3.29–9.11)
Smitten [14] 2008 USA 1/1999–7/2006 Retrospective	RA patients (n=24,530) compared with 500,000 non-RA patients	PEQ ≤ 5 6–10 >10	Any infection requiring hospitalization	Increased risk of infection; dose dependent	RR of hospitalization for infection risk as per PEQ • PEQ ≤ 5, RR 1.32 (95% CI 1.06–1.63) • PEQ = 6–10, RR 1.94 (95% CI 1.53–2.46) • PEQ >10, RR 2.98 (95% CI 2.41–3.69)

Author Year Country Duration Study type	Population	Prednisone or PEQ dose	Infections	Results	Risk Ratios±
Greenberg[38] 2010 USA CORRONA 10/2001–9/2006 Prospective	Patients with RA on DMARDs n=7,971	PEQ <10 PEQ > 10	Overall infections (includes both Opportunistic and non-opportunistic infections)	Increased risk of overall infections with PEQ>10	IRR of overall infections as per PEQ • Any dose: IRR 1.05 (95% CI 0.97–1.15) • PEQ > 10: IRR 1.30 (95% CI 1.11–1.53) IRR of opportunistic infections: Any CS dose: IRR 1.63 (95% CI 1.20–2.21)
Dixon [31] 2012 Quebec 1985–2003 Nested case-control	RA >65 years old n=16,207	PEQ <5 PEQ 5–9.9 PEQ 10–14.9 PEQ 15–19.9 PEQ ≥20	Non-serious infections	Increased risk of non-serious infections if PEQ>5; dose-dependent	Adj rate ratio of non-serious infections • PEQ <5, RR 1.1(95% CI 0.99–1.22) • PEQ 5–9.9, RR 1.1(95% CI 1.04 −1.16) • PEQ 10–14.9, RR 1.25 (95% CI 1.17–1.34) • PEQ 15–19.9, RR 1.26 (95% CI 1.12–1.42) • PEQ ≥20, RR 1.85 (95% CI 1.68–2.05)
Dixon [20] 2011 N/A Up to 1/2010 Meta-analysis	21 RCTs 42 observational studies	Any dose	Any Infection	CS therapy was associated with increased risk of infection in Observational studies, not in RCTs	RR of increased infection risk as per PEQ • In RCTs: RR 0.97 (95% CI, 0.69, 1.36) • In observational studies: RR 1.67 (95% CI 1.49, 1.87)
G. Grijalva [30] 2011 USA 1998–2007 Retrospective	1- RA, n=10,484 2- Pso or SpA, n= 3215	Any dose	Infection requiring hospitalization In patients on DMARDs	Increased risk of infection; dose-dependent in RA group and Pso/SpA group	HR of serious infection risk as per PEQ • RA group: PEQ 0 -<5, HR 1.32 (95% CI 1.10–1.58) PEQ 5–10, HR 1.78 (95% CI 1.47–2.15) PEQ >10, HR 2.95 (95% CI 2.41–3.61) • Pso and SpA group: 0- <5 1.15 (0.75–1.77) 5–10 2.01 (1.08–3.73) > 10 2.77 (1.44–5.32)
Xie, W.L. [39] 2012 China 1/2009–2/2011 Retrospective	RA n=2,452	Any dose	Nosocomial infections	Increased risk of infection	• OR of nosocomial infections by multivariate analysis: 1.02 (95% CI 1.01– 1.03)

Author Year Country Duration Study type	Population	Prednisone or PEQ dose	Infections	Results	Risk Ratios±
Van Dartel[40] 2013 DREAM 2005–2010 Prospective	Patients with RA n=2,044	Any dose	SBI	Increased risk of infection	• HR of SBI by multivariate analysis HR 1.54 (95% CI 1.08,2.20) • HR of SBI by univariate analysis HR 1.78 (95% CI 1.26, 2.53)
Widdifield [34] 2013 Ontario 1992–2010 Nested case control	RA ≥ 66 Y/O n=86,039	PEQ ≤5 PEQ 6–9 PEQ 10–19 PEQ ≥20	Serious infections	Increased risk of infection; dose dependent	Adj OR of serious infections as per PEQ: • PEQ ≤5, OR 3.96 (95% CI 3.67–4.27) • PEQ 6–9, OR 4.28 (95% CI 3.70–4.96) • PEQ 10–19, OR 5.98 (95% CI 5.42–6.59) • PEQ ≥20, OR 7.57 (95% CI 6.87–8.34)

± Hazard Ratio (HR), Odd Ratio (OR), Incidence Rate Ratio (IRR) where indicated.

adj, adjusted; CORRONA, Consortium of Rheumatology Researchers of North America registry; CS, corticosteroids; DMARD, disease modifying anti-rheumatic drugs; DREAM, Dutch Rheumatoid Arthritis Monitoring Registry; MTX, Methotrexate; NOAR, Norfolk Arthritis Register; PEQ, prednisone equivalent dose measured by mg/day; Pso, Psoriasis; RA, rheumatoid arthritis; SBI, serious bacterial infections; SpA, Spondyloarthritis; TNF, tumor necrosis factor inhibitors; Y/O, years old.

Table 3

Prevention strategies

Disease	Prevention strategies
Influenza	Annual vaccination in those with rheumatic diseases [88].
Herpes zoster	Vaccine in all patients with rheumatic diseases age ≥ 50 [75, 77, 78].
Pneumococcal pneumonia	In patients without prior vaccination, one dose of PCV13 in those on chronic steroid therapy should be given followed by PPSV23 ≥ 8 weeks later. A second dose of PPSV23 is indicated 5 years after first dose. [88].
Pneumocystis jirovecci pneumonia	Treatment with trimethoprim/sulfamethoxazole (160 mg/800 mg) three times a week if on PEQ>16 mg daily for more than 8 weeks [45].
Tuberculosis (TB)	Screening for latent TB using either TST or Interferon gamma release assays* in those anticipated to start long term corticosteroid therapy (10 mg for at least one month) and treat for latent TB if positive [81]. If already on chronic steroid therapy, screen with Interferon gamma release assay and be aware of risk of false negatives with TSTs or IGRAs.

Interferon gamma release assays=IGRAs, 13-valent pneumococcal conjugate vaccine=PCV13, 23-valent pneumococcal polysaccharide vaccine=PPSV23, tuberculin skin tests=TST

* Interferon gamma release assay is preferred if patient has a history of BCG vaccine