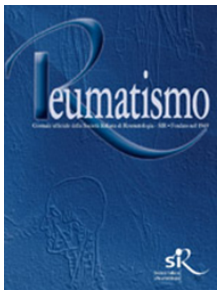

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To prophylax or not to prophylax? The role of trimethoprim/sulfamethoxazole as a prophylactic agent in systemic vasculitis: the case of antineutrophil cytoplasmic antibody-associated vasculitis and giant cell arteritis

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Summary
Inflammatory rheumatic and musculoskeletal diseases, including systemic vasculitis, increase the risk of infection due to immunosuppressive treatments and disease-related immune dysfunction. In this viewpoint, we focused on patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV) and giant cell arteritis (GCA). We critically reviewed the literature on infectious risks and the role of trimethoprim/sulfamethoxazole (TMP/SMX) as a prophylactic agent in these conditions. In AAV, serious infections from opportunistic (*e.g.*, *Pneumocystis jirovecii*) and non-opportunistic pathogens are especially common, peaking in the first year post-diagnosis. TMP/SMX is crucial for prevention, as its use significantly reduces the incidence of *Pneumocystis jirovecii* pneumonia (PJP) and other serious infections. In GCA, although the risk of PJP is low, the overall infection risk is high and correlates with glucocorticoid dosage. However, evidence supporting the routine use of TMP/SMX in GCA is limited, warranting further investigation through randomized clinical trials.

Introduction

Inflammatory rheumatic and musculoskeletal diseases (iRMDs) are associated with an elevated risk of infection, that is not only attributed to treatment with immunosuppressive agents but also to the disturbance of the immune system by the disease itself. While there is considerable experience from large cohort studies on the prevalence of infections in rheumatoid arthritis and other common iRMDs (1), data on systemic vasculitis are scarce and limited by heterogeneous populations and different study designs. Understanding the risk and burden of infectious complications is essential for developing preventive strategies and determining which patients require antimicrobial prophylaxis.

In this viewpoint, we conducted a critical review of the literature on infectious risk in systemic vasculitis, taking into account the lights and shadows of trimethoprim/sulfamethoxazole (TMP/SMX) as a prophylactic agent in patients with antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) [comprising granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA)] (2) and giant cell arteritis (GCA). While TMP/SMX has traditionally been known for its effectiveness primarily in preventing *Pneumocystis jirovecii* pneumonia (PJP), it is now crucial to re-evaluate its wider range of potential applications. Our discussion on TMP/SMX will extend beyond PJP prophylaxis, encompassing its preventive role against a wide range of infections.

Antineutrophil cytoplasmic antibody-associated vasculitis

The scale of the problem

Infections are a major cause of morbidity and mortality in AAV (3, 4). A recent systematic literature review (SLR) and meta-analysis, encompassing 2938 people with AAV, revealed an overall cumulative incidence of serious infections in 16% of patients [95% confidence interval (CI): 6.9-27.5%] (5). Notably, patients receiving cyclophosphamide and azathioprine exhibited a higher incidence of serious infections [20.8% (95% CI: 4.6-43.7%)] than those treated with rituximab in both the induction and maintenance phase [14.1% [95% CI: 5.2-26.0%)] (5).

The cumulative incidence of severe infections was higher during the first 12 months after diagnosis (22 infections/patient-year as compared to 9.1 when considering the total follow-up), largely because of increased disease activity and intensive immunosuppressive treatment, including high glucocorticoid doses. Intrinsic factors, such as the type of organ involvement, advanced age, and comorbidities, also significantly contribute to the risk of infection (3). Infections significantly impact the quality of life of patients and are one of the leading causes of hospitalization (6). They also represent the primary cause of death, both in the first year post-diagnosis as well as in the long-term (4, 7), as shown in Figure 1.

Airways infections, particularly those affecting the lower respiratory tract, constitute the majority of severe infections in this context (5), while opportunistic infections, despite immunosuppression, have become relatively rare in recent years, accounting for only 6% of all severe infections (3).

Pneumocystis jirovecii pneumonia prophylaxis

The relatively low incidence of opportunistic infections, including PJP, in patients with AAV can likely be attributed to improved patient management, especially in terms of optimization of immunosuppressive treatment strategies (4). While several non-pharmacological risk factors for PJP have been identified over time (such as interstitial lung disease, renal failure, T cell depletion or dysfunction, advanced age, and other rheumatic diseases), immunosuppressive therapies, particularly chronic intake of glucocorticoids, play a pivotal role (5, 8-10). A retrospective study on iRMDs, spanning 12 years and published in 1999, included 31 GPA patients treated with high cumulative doses of glucocorticoids, reporting PJP incidences as high as 12% (11). In contrast, in a retrospective analysis of 437 AAV patients from 2021, a statistically significant difference was observed in the incidence of PJP: 4.9% among patients not receiving TMP/SMX prophylaxis compared to just 0.7% in those who received it ($p<0.001$) (12). Another recent retrospective study based on a health records database in northern California confirmed this trend, reporting no PJP cases over 640 patient-years

(13). This study, however, was limited by a small sample size as it included only 47 patients with GPA and 21 with MPA.
Several additional retrospective studies support the efficacy of TMP/SMX in reducing the incidence of PJP [adjusted hazard ratio (aHR)=0.07 (95%CI 0.01-0.53)] and mortality related to this disease, irrespective of the glucocorticoid dose or other medications used (14-16). In this context, the study by Nettleton *et al*., published in 2023, stands out as an exception. In this retrospective analysis of 1461 patients with AAV receiving induction therapy with rituximab (69.7%), cyclophosphamide (18.9%), or both (11.4%), 40.7% received PJP prophylaxis within the first 30 days. However, the incidence of PJP during induction therapy was similar between those who received prophylaxis and those who did not (16.1 *vs*. 14.4 per 1000 person-years, respectively) (17). However, there are several potential confounders in this study. First, only data on physicians' TMP/SMX prescriptions, rather than actual drug intake, are available; second, prescribers may have considered PJP prophylaxis only in those with the highest risk for PJP (bias by indication); third, prophylaxis exposure was very short, limiting the sensitivity to detect any differences between groups. Nevertheless, this and other studies raise an important question: has the incidence of PJP in AAV become so low that the potential risks of TMP/SMX, including hematologic, neurologic, and hypersensitivity reactions, outweigh the benefits (18)? On the other hand, most side effects of TMP/SMX have been reported when the drug is used at therapeutic dosages (*i.e*., 160 mg/800 mg twice a day), while they appear much rarer when it is used at prophylactic doses (19). A large retrospective study on hematologic and rheumatologic patients treated with rituximab comparing those receiving TMP/SMX prophylaxis to those who did not showed that the number needed to harm was 101 (61.9-261.1) in that population while the number needed to treat to prevent one PJP case was only 32 (24.8-39.4) (20). These findings underscore the crucial point that the potential benefits of TMP/SMX prophylaxis in patients at risk outweigh the risks of adverse events. A selection of the studies on iRMD cited here are summarised in Table 1.

Trimethoprim/sulfamethoxazole prophylaxis: only a matter of Pneumocystis jirovecii pneumonia?
While TMP/SMX has traditionally been used to prevent PJP infections, it seems also effective in reducing the risk of non-PJP infections (16, 21, 22). A *post-hoc* analysis of the RAVE trial (Rituximab *versus* Cyclophosphamide for ANCA-Associated Vasculitis), including 197 GPA or MPA patients with a follow-up of 531 days (range: 2-581), showed that TMP/SMX significantly reduce the overall risk of severe infections requiring intravenous antibiotics or posing a life-threatening risk [hazard ratio (HR): 0.232; 95% CI: 0.09-0.62; p=0.004]. Notably, this effect was equally observed in patients treated with either rituximab (HR: 0.20; 95% CI: 0.05-0.77; p=0.019) or cyclophosphamide (HR: 0.232; 95% CI: 0.06-0.88; p=0.032) (21). In a large retrospective, multicenter study involving 919 GPA patients treated with rituximab and a mean follow-up of 496 days, TMP/SMX also protected against the occurrence of severe (aHR 0.5; 95% CI 0.3-0.8) and non-severe infections (aHR 0.7; 95% CI 0.5-0.9) (23).

When, how long, how much?
Based on the available evidence, the majority of international recommendations advocate for the use of TMP/SMX as a prophylactic agent in patients with AAV, not only to protect against PJP but also to prevent severe infections in general, especially in patients receiving rituximab, cyclophosphamide, or high doses of glucocorticoids (>30 mg/day for more than 4 weeks) (24-26). European Alliance of Associations for Rheumatology recommendations suggest continuing prophylaxis for at least three months after the last administration of cyclophosphamide and six months after rituximab (26).
Despite the evidence available and the international recommendations clearly favoring the use of TMP/SMX, in clinical practice, only a minority of patients actually receive prophylaxis. Thorpe *et al*., in their retrospective analysis of 14798 newly treated patients with AAV from the Medicare database, found that only 29% of those with an indication for TMP/SMX prophylaxis actually received this drug (27).

Regarding TMP/SMX dosage, a 2007 SLR found no difference in efficacy for PJP prevention between a thrice-weekly dose of 160 mg/800 mg and a daily dose of 80 mg/400 mg (10).
TMP/SMX use can cause side effects ranging from mild reactions like skin rash, nausea, and dizziness to severe conditions such as Stevens-Johnson syndrome, hematologic abnormalities (primarily anemia and agranulocytosis), electrolyte imbalances (mainly hyperkalemia), and renal failure. Additionally, special caution should be used in pregnant women, patients with glucose-6-phosphate dehydrogenase deficiency or sulphas allergies, in whom TMP/SMX should be avoided. Finally, TMP/SMX has interactions with several drugs, including warfarin, sulfonylureas, meglitinides, methotrexate, nonsteroidal anti-inflammatory drugs, angiotensin receptor blockers, and angiotensin-converting enzyme (ACE) inhibitors (18). Hence, when prescribing TMP/SMX, careful monitoring and evaluation of other ongoing drugs should be undertaken. Monitoring should include regular complete blood counts, electrolyte levels, and renal function tests, especially for patients with renal impairment or those on interacting medications. If TMP/SMX is contraindicated or side effects are documented, the prescription of alternative medications should be considered. These include atovaquone, pentamidine and dapsone (28).
The use of antibiotics inevitably carries a significant risk of inducing resistance, potentially leading to the selection of more aggressive pathogens (29). This risk should not deter the prescription of TMP/SMX but should encourage careful patient selection, reserving prophylaxis for those at higher risk.

Giant cell arteritis

Do patients with giant cell arteritis have an increased risk of infections?

Infections are a significant factor of morbidity also in GCA, where older age (usually patients are >50 years old) and the extensive use of immunosuppressive agents, particularly glucocorticoids, make the ground fertile for different pathogens (30, 31). Until the publication of the GIACTA trial (32), glucocorticoids were the most important treatment option in GCA (with limited steroid-sparing effects of methotrexate) (33). Glucocorticoids were typically tapered slowly, aiming for a dose of 5 mg prednisone-equivalent per day after one year, with discontinuation planned after 18-24 months. However, observational studies indicate that they are often used for much longer, leading to high cumulative doses in most patients (34). It is well known that glucocorticoids are a major driver of infection risk, both directly through their immunosuppressive effects and indirectly by promoting comorbidities such as diabetes and osteoporosis (35). With the availability of tocilizumab, the treatment approach shifted towards minimizing glucocorticoid use, especially in patients at high risk for glucocorticoid-related adverse events. However, most studies on infections in GCA were conducted before tocilizumab became available (Table 1).
The study with the best quality focusing on the risk of infections in GCA is a prospective study conducted at several French medical centers between 1991 and 2009. This study included 486 patients with GCA and an equal number of age- and sex-matched healthy controls followed up for 5 years (36). The risk of severe infections was higher in the GCA than in the control group but only during the first 12 months, confirming the link between infections and high glucocorticoid doses used at the disease outset. Concerning the type of infections, pyelonephritis and lower tract respiratory infections (LRTI) were the most common severe infections overall; however, only septic shock and colitis were more common in GCA patients than in controls. The detrimental effects of glucocorticoids manifested also in the long term. A sub-analysis of the study comparing GCA patients using ≥10 mg or <10 mg prednisone equivalent per day after one year revealed that patients in the higher dose group still had an increased risk of severe infections. Besides, the authors observed a higher rate of severe infections in GCA patients at older age.
Advanced age (≥70 years) and higher cumulative glucocorticoid doses were identified as risk factors for infections (not limited to severe infections) in a recent Danish nationwide cohort study focusing on the first year post-diagnosis (37).

An important contribution comes from a case-control study using a UK national database (1987-2007), where newly diagnosed GCA patients were matched with up to six controls without GCA or any autoimmune disease, matched by age, sex, and index date (38). Over an observational period of more than 3 years, approximately half of GCA patients (48%) and one-third (37%) of non-GCA patients experienced at least one systemic infection. Patients with GCA had a significantly higher risk of LRTI, urinary tract infections, and serious infections than controls. Notably, in GCA patients, the highest risk for LRTI, serious infections, and sepsis was observed during the first 6 months after diagnosis, which might be explained by the higher glucocorticoid dosages administered in early stages of the disease.

Real-world data investigating the risk of infections in GCA patients treated with tocilizumab are scarce. A retrospective analysis of a Spanish multicenter cohort of 134 GCA patients revealed an annual incidence of serious infections in tocilizumab users that was comparable to that reported in former studies on glucocorticoid monotherapy. Besides, it confirmed the intriguing role of age and glucocorticoids as risk factors for infections (39).

Do patients with giant cell arteritis have an increased risk of Pneumocystis jirovecii pneumonia?

All the studies cited in the previous paragraph share a common finding: the scarcity of reported PJP cases among GCA patients. This suggests that the risk of PJP in people with GCA is quite low, in contrast with patients with AAV. However, very few studies investigated specifically the incidence of PJP in patients with GCA.

Only one prospective study has specifically examined the risk of PJP in GCA, following a cohort of 62 consecutive patients and documenting PJP in four cases (40). While the sample size is certainly small and prone to bias, the incidence is much higher than expected. All four patients were on methotrexate and in three cases, the cumulative prednisone dose was higher than the average dose in that cohort. In addition, in this study, the authors found that 75% of GCA patients with PJP (*i.e.*, three out of four) had lymphocytopenia (<400/μL) compared to 9% of the remaining patients. Notably, only 19% of patients received PJP prophylaxis. The authors concluded that PJP prophylaxis should be considered in patients with GCA, particularly in those at risk (*e.g.*, long-term moderate-to-high dose glucocorticoid users, concomitant methotrexate, lymphocytopenia).

Prior to this report, a retrospective study was published analyzing 7543 patients evaluated for suspected GCA over a 32-year period. Only seven cases of PJP were identified in this cohort (41). One of these had concurrent myelodysplasia, and one had interstitial lung disease, both known predisposing factors for PJP. Additionally, all patients developed PJP while on high-dose glucocorticoids (*i.e.*, ≥30 mg daily of prednisone-equivalent). Four of them developed PJP while they were on high-dose glucocorticoids for ≥4 months, which does not anymore correspond to current clinical practice. One point to consider is the fact that PJP prophylaxis in commonly used in the USA even for non-AAV patients (42). This might have led to a lower PJP incidence in that cohort (even though prophylaxis was not specifically reported). Nevertheless, we still can conclude that PJP is less of a problem in GCA, if compared with AAV, and is usually associated with exceptional concomitant situations.

Similarly, another retrospective study from a US national health database found no cases of PJP among 1168 patients with GCA in the first 6 months after diagnosis, even though only 7% of patients had received PJP prophylaxis (43).

Current treatment recommendations for the management of GCA still have not included a statement about PJP prophylaxis (30). This is likely because of the scarcity of data and the perception by the scientific community that PJP in GCA patients rarely occurs in clinical practice.

It should be noted that none of the studies cited in this section included an adequate number of patients treated with tocilizumab to investigate the impact of this treatment on the risk of PJP. However, studies conducted on other rheumatic diseases have not observed and association between tocilizumab treatment and PJP (44).

Is there a rationale for infectious prophylaxis in patients with giant cell arteritis?

Apart from the absence of solid evidence supporting the use of antibiotics to prevent infections in GCA, the extensive use of these drugs carries its own risks. As stated previously, TMP/SMX may lead to hypersensitivity reactions, agranulocytosis, hemolytic anemia, and hepatotoxicity. Besides, there are several drug interactions with medications commonly used in the elderly population, such as warfarin or ACE inhibitors. These interactions are certainly more relevant for therapeutic doses of TMP/SMX (18), and PJP prophylaxis might, therefore, still be associated with a reasonable benefit/risk ratio when the estimated probability for the occurrence of this infection is >3.5% (10). Most studies indicate a low risk of PJP in GCA, which suggests that TMP/SMX prophylaxis may not be warranted for these patients. However, the experience in AAV is that TMP/SMX can also prevent other opportunistic and non-opportunistic infections. Available literature indicates that the risk of infections is unequivocally high in patients with GCA, at least in the first stages of the disease. Therefore, it would be tempting to investigate whether antibiotic prophylaxis could reduce the overall risk of infections in GCA. The ideal study design to address this question is a randomized clinical trial involving new-onset GCA patients assigned to either a TMP/SMX prophylaxis or placebo group. Monitoring the incidence of serious and non-serious infections, along with the rate of adverse events, would help evaluate the risk-benefit trade-off of using this drug in GCA.

Conclusions

Infections significantly contribute to the disease burden in both AAV and GCA. In AAV patients, PJP is a major infectious complication, but other serious bacterial infections are also common. Evidence strongly supports TMP/SMX prophylaxis in this population, not only to prevent PJP but also to reduce the risk of other severe and non-severe infections. Therefore, we firmly believe that PJP prophylaxis is essential in managing AAV and should be initiated at the start of induction therapy and continued throughout the disease course, in line with international recommendations. Compared to AAV, PJP seems to be a less common complication in patients with GCA. This might be explained by the fact that strong immunosuppressive agents such as rituximab and cyclophosphamide are normally not used to treat this disease (30). Besides, GCA almost never affects the lungs, and compromised lungs are more prone to PJP (31). On the other hand, GCA patients are highly susceptible to other infections, but evidence of whether antibiotic prophylaxis may help to prevent these complications is still missing. Therefore, in our clinical practice, we do not routinely prescribe antibiotic prophylaxis for GCA patients, especially since most are treated with tocilizumab and receive high doses of glucocorticoids only for short durations (30, 32). Given the limited data currently available, the only situations in which we would recommend considering the introduction of PJP prophylaxis would be in patients with pre-existing chronic lung disease or with contraindications to tocilizumab and a need for high doses of glucocorticoids for prolonged periods of time.

In the future, efforts should certainly be made to consolidate the use of TMP/SMX prophylaxis in patients with AAV in daily clinical practice. On the other hand, it will be necessary to find a definitive and solid answer to the question of whether prophylaxis is really necessary in patients with GCA.

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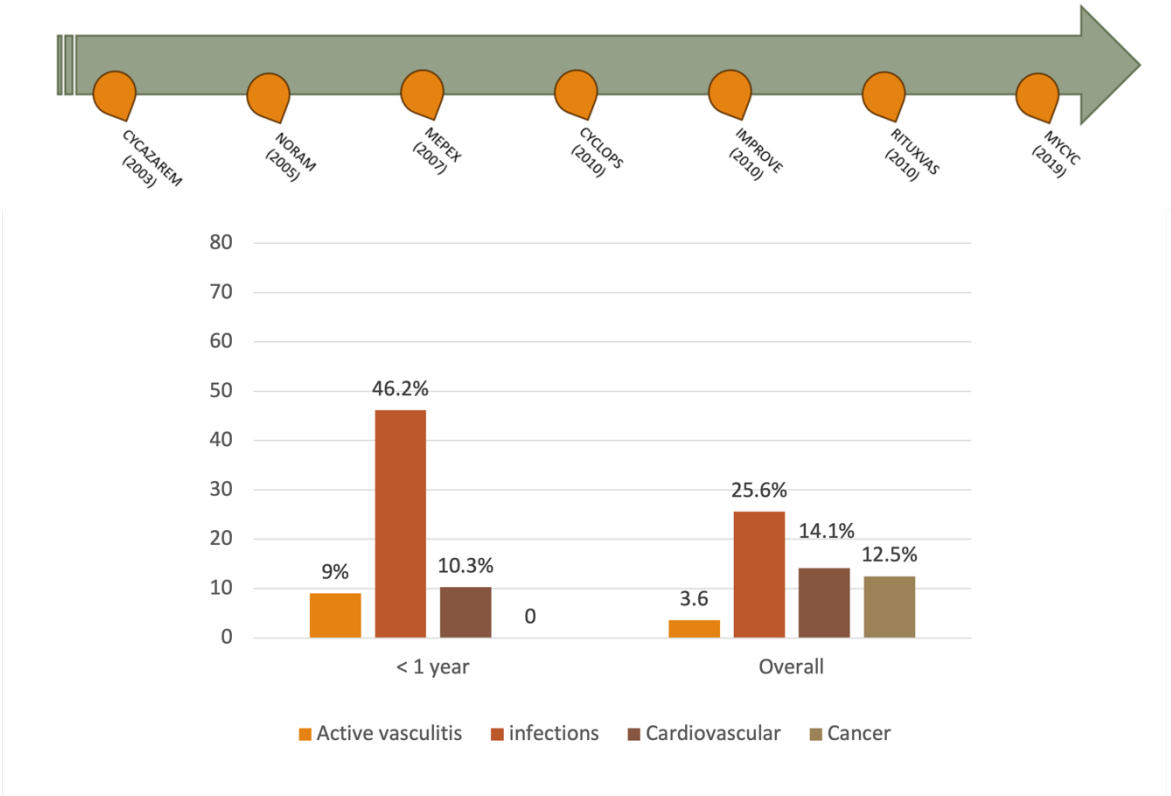

Figure 1. Impact of infections on mortality in antineutrophil cytoplasmic antibody-associated vasculitis trials (data from Sánchez Álamo *et al*., Nephrol Dial Transplant 2023).

Table 1. Main studies on the risk of *Pneumocystis jiroveci* pneumonia and the role of trimethoprim/sulfamethoxazole prophylaxis in antineutrophil cytoplasmic antibody-associated vasculitis and giant cell arteritis.

Author, year	Type of study	Population	Main results	Ref.
ANCA-associated vasculitis				
Krombichler *et al.*, 2018	Retrospective	N=192 (AAV) TMP/SMX (n=73) *vs*. no TMP/SMX (n=119)	↓ frequency of severe infections (HR= 0.30; 95% CI 0.13-0.69)	(16)
Park *et al.*, 2018	Retrospective	N=470 (iRMD); N=58 (AAV) TMP/SMX (n=262) *vs*. no TMP/SMX (n=1260) treatment episodes	↓ 1 year PJP incidence (aHR=0.07; 95% CI 0.01-0.53) and PJP related mortality (aHR=0.08; 95% CI 0.0006-0.71)	(15)
Schmajuk *et al.*, 2019	Retrospective	N=316 (iRMD); N=68 (AAV) TMP/SMX (n=124) vs no TMP/SMX (n=192) prophylaxis	No PJP infections in both groups	(13)
Honda *et al.*, 2021	Retrospective	N=437 (iRMD); N=77 AAV) TMP/SMX (n=376) *vs* no TMP/SMX (n=61) prophylaxis	PJP incidence in TMP/SMX vs no TMP/SMX 0.7% vs 4.9% (p<0.001)	(12)
Nettleton *et al.*, 2023	Retrospective	N=1461 (AAV) PJP (n=595) vs no PJP (n=872) prophylaxis	16.1 vs 14.1/1000 PY. In TMP/SMX pts: ↑ risk of leukopenia (HR 3.1; 95% CI 1.1–8.6), rash (HR 1.9; 95% CI 1.0–3.6), and nephropathy (HR 2.6; 95% CI 1.3–5.1)	(17)
Odler *et al.*, 2023	Post-hoc analysis (RAVE trial)	N=197 (AAV) AAV patients with severe infections (n=175) *vs* no severe infections (22)	TMP/SMX prophylaxis reduced severe infections (HR: 0.232; 95% CI 0.087-0.623)	(21)
Mendel *et al.*, 2024	Retrospective	N=919 (AAV treated with RTX) TMP/SMX (n=281) vs no TMP/SMX (n=638) prophylaxis	TMP/SMX protected against severe (aHR 0.5; 95% CI 0.3-0.8) and non-severe infections (aHR 0.7; 95% CI 0.5-0.9)	(22)
Giant cell arteritis				
Kermani *et al.*, 2011	Retrospective	N=7543 (suspected GCA)	7 cases of PJP identified TMP/SMX prophylaxis not reported	(41)
Berger *et al*, 2015	Prospective	N=62 (GCA)	4 cases of PJP identified TMP/SMX prophylaxis in 19% of patients	(40)
Anumolu *et al.*, 2023	Retrospective	N=1168 (GCA)	No cases of PJP TMP/SMX prophylaxis in 7% of patients	(43)

aHR, adjusted hazard ratio; AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; CTD, connective tissue disease; GCA, giant cell arteritis; GPA, Granulomatosis with polyangiitis; iRMD, inflammatory rheumatic diseases; N, number; pts, patients; PJP, Pneumocystis jirovecii; PY, person/year; Ref., reference; RTX, rituximab; TMP/SMX, trimethoprim/sulfamethoxazole.