Pneumocystis jiroveci Prophylaxis with Rituximab

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Abstract

Introduction: *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis is highly effective in HIV patients. The objective of this study was to examine the efficacy and adverse effects of PJP prophylaxis among rituximab treated non–HIV patients.

Methods: We performed a systematic review based on the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) model.

Results: Eight retrospective studies were included with a combined cohort of 6048 patients. The most common prophylaxis drug used was trimethoprim/sulfamethoxazole (TMP-SMX). There were 17 PJP infections in the prophylaxis arm against 147 in the control arm (incidence 0.3% *vs* 2.4%; OR, 0.35; 95% CI, 0.19-0.64). The number needed to treat (NNT) to prevent 1 PJP episode was 36 patients (CER, 3.6%). The mortality rate due to PJP was 25%. All ADRs (adverse drug reactions) resolved with TMP-SMX discontinuation.

Conclusion: Prophylaxis with TMP-SMX seems justifiable in combined therapies with rituximab. But in monotherapy, the results are not robust. The decision should be patient-based. The optimal duration of prophylaxis is also unclear.

Keywords: Pneumonia, Pneumocystis/drug therapy; Rituximab/therapeutic use; Trimethoprim, Sulfamethoxazole Drug Combination/therapeutic use

INTRODUCTION

Pneumocystis jiroveci pneumonia (PJP) prophylaxis is highly effective when done properly.[1,2]

In HIV patients, where most of our knowledge comes from, trimethoprim-sulfamethoxazole (TMP-SMX) is the first-choice agent as it offers 89% to 100% protection rates.[3-6]

TMP-SMX is also highly effective in non-HIV patients where PJP is associated with intense pulmonary inflammation, severe hypoxemia and higher mortality rates, 30% to 60% *vs* 10% to 20% in HIV patients.[7-12]

Prophylaxis should be considered in any non-HIV immunocompromised patient when the risk of developing PJP is above 3.5% to 6.2%, based on the comparison of the number needed to treat (NNT) to number needed to harm (NNH) or controlled event rate.[13,14] Besides these numbers, we must look at the risk-benefit and cost-effectiveness analyses, for it to be a well-weighted decision.[7]

Most of the PJP prophylaxis data in non-HIV patients comes from specific populations, like hematologic malignancies, bone marrow and solid organ transplant recipients.[8,14]

In glomerular diseases, there is no data specifying the etiology.[7] Indications for therapy are mainly based on the immunosuppressive therapy used, with formal indication for cyclophosphamide, as used in some anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis and systemic lupus erythematosus patients.[7] Two retrospective studies also suggested benefit in prophylaxis when prednisone is used for at least 30 mg/day for at least 4 weeks as used in some primary glomerular diseases.[15,16]

When looking specifically at immunosuppression with rituximab, there is a lack of evidence on the measurement of risk *versus* benefits of the PJP prophylaxis, which brings some doubts about its use.[7,17] Regarding combined therapy, several reports exist of PJP in patients receiving rituximab in combination with corticosteroids.[10,18]

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Rituximab is a monoclonal antibody that leads to a depletion of B cells. On the other hand, PJP is associated with T cell suppression.[17] Regardless of this, some data associates rituximab combined with chemotherapy with a higher prevalence rate of PJP.[19-26] It was also shown, in a murine study, that rituximab can impair type ll responses that lead to a dysregulated CD4+ T cell function.[27] Another study showed the critical role that B cells perform in CD4+ T cell activation.[28] Furthermore, rituximab can be associated with a prolonged hypogammaglobulinemia and with an impaired plasma cells production. All factors that interfere with the *Pneumocystis jirovecii* killing process.[27,29]

The need for PJP prophylaxis in rituximab monotherapy is unknown.

The objective of our systematic review was to examine data regarding the efficacy and adverse effects of PJP prophylaxis among non–HIV patients treated with rituximab, namely on monotherapy.

METHODS

We performed a systematic review and meta-analysis of studies that compared any antibiotic with a known effect against *Pneumocystis jirovecii* to no treatment in non-HIV patients treated with rituximab.

Search Strategy

We used the following search string to identify trials: “rituximab”, “pneumocystis”, “prophylaxis”.

Study Selection

We included patients with hematologic diseases, rheumatic diseases, pre/post-solid organ transplantation and pemphigus patients. We have included patients in rituximab monotherapy and with other chemotherapy adjuvants, including azathioprine, mofetil mycophenolate, methotrexate, IVIg, cyclophosphamide, dapsone, prednisolone and R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone).

Main Outcome Variables

The primary outcome was PJP incidence in the prophylaxis versus control group. Secondary outcomes included PJP-related mortality at end of study follow-up and adverse events of treatment in both groups.

Analysis

Two reviewers independently screened the trials for inclusion or exclusion to the review, extracted the data, and assessed the methodological quality of the included trials. We used the random-effects model throughout the review. ROBINS-I risk-of-bias tool was used for bias assessment. When no events occurred in treatment and control arm, the study was omitted from analysis. The number needed to treat (NNT) was calculated as 1/absolute risk reduction. Heterogeneity and homogeneity between trials were assessed using a chi-squared test (p<0.10) and the I^2 measure of inconsistency.

RESULTS

Study Selection

The PRISMA flowchart is presented in Fig. 1. Eight studies, conducted from 2002 to 2021, were included. All studies were retrospective. No randomized controlled studies were identified. Low risk of bias was calculated according to ROBINS-I tool. A total of 6048 patients were evaluated.

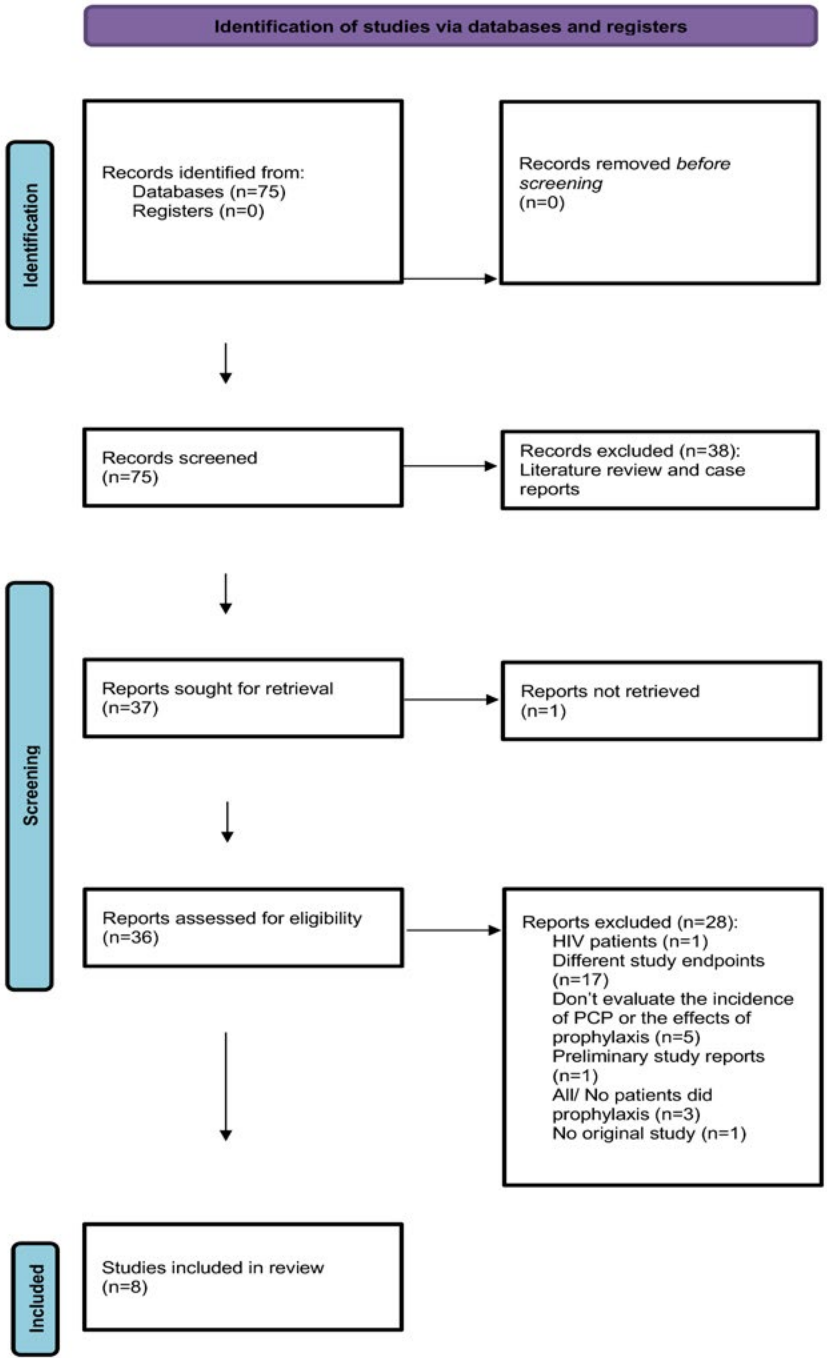

Figure 1. PRISMA flow diagram of study selection

Study Characteristics

Inclusion and exclusion criteria of the included studies are detailed in Table 1. Table 2 provides a summary of the studies' characteristics and outcomes.

PJP Definition

In all studies, except one PJP diagnosis criteria are specified and include clinical and radiological aspects and microbiology.[21,30-36] One study separated patients into definite PJP and probable PJP, differentiated by microbiological confirmation.[33] In three studies an additional criteria was response to therapy and two studies had the processes reviewed by an infectious disease expert.[30-32,36]

Adverse Events (AEs) and Adverse Drug Events (ADRs)

Five studies reported AEs.[31-34,36]

Two studies reported ADRs. In these studies, all AEs were captured and then the probability of causation of each AE was estimated by one author based on timing, known

AE profile, and improvement of AE after cessation of the agent. AEs showing probable/likely or certain causality were regarded as ADRs related to TMP-SMX.[30,31]

The severity of each AE/ADR was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE).

Table 1. Inclusion and exclusion criteria

Trial	Inclusion Criteria	Exclusion Criteria
Park 2022[30]	Rituximab for the first time between 2002 and 2018 at Seoul National University Hospital. Hematologic, rheumatic and pre/post-solid organ transplantation patients.	Previous history of PJP Age <18 years Follow-up < 28 days HIV infection, primary CNS angiitis or multiple sclerosis
Raso 2021[34]	Patients with ITP. At least one dose of rituximab from January 2008 to June 2018 at five Italian hematology centers.	Age <18 years
Catroux 2017[35]	At least one rituximab perfusion between 2006 and 2014 at Poitiers University Hospital.	Lymphoma, monoclonal gammopathy, hematologic neoplasms and graft rejection
Hardak 2012[21]	Newly diagnosed DLBCL. R-CHOP between December 2004 and December 2010. Patients in complete remission for a minimum of 6 months.	Death from non-infectious causes in the first 6 months post-therapy Age <18 years
Lee 2021[33]	At least one cycle of R-CHOP for DLBCL at Seoul National University Bundang Hospital, between May 2004 and January 2019.	Age <18 years
Faraji 2021[36]	Autoimmune Bullous Diseases Research Center, Iran receiving rituximab from 2016 to 2018.	Not reported
Hsu 2023[32]	Pemphigus patients. Rituximab for the first time between 2008 and 2021 at a tertiary referral center in northern Taiwan.	Not reported
Park 2023[31]	Rheumatic diseases receiving rituximab for the first time between 2004 and 2020 at 3 medical centers in South Korea.	Previous history of PJP Age <18 years Follow-up < 28 days Malignancy, neurologic disease, or solid organ recipients

*RCHOP regime consists of 375 mg/m² rituximab, 750 mg/m² cyclophosphamide, 50 mg/m² doxorubicin, and 2 mg vincristine on day 1, as well as 100 mg prednisone on days 1–5, CNS- central nervous system, ITP- immune thrombocytopenia, DLBCL- diffuse large B cell lymphoma.

Table 2. Summary of the included studies

Trial	Number and Type of Patients	Combination therapies	Median Follow up	PJP and PJP-related outcomes	Adverse Reactions
Park 2022[30]	3,524 patients: - Control (N=2523;59%) - Prophylaxis (N=1001;40 %) Hematologic disease, rheumatic disease, and pre/post-solid organ transplantation patients.	Concomitant treatment: - corticosteroids 27%. - Previous chemotherapy 2%.	12 months	- PJP incidence: 3% control *vs* 1% prophylaxis: N= 80 control *vs* N=12 prophylaxis (11 post-therapy)) - Risk factors for PJP: Azotaemia, high-dose steroids - Median time for PJP: 86 days. - ICU admission: 35% (78% control *vs*22% prophylaxis) - Mechanical ventilation: 30% (75% control *vs* 25% prophylaxis). - PJP mortality: 27% (25/92). - Prophylaxis significantly reduced 1-year PJP. incidence and mortality, in all disease groups (*p* value <0.001). - Prophylaxis >20 weeks showed greater prophylactic effect. - NNT global: 32 (17 high-dose steroids *vs* 46 others). -Most PJP cases (15 of 16) in patients exposed to prophylactic TMP-SMX occurred a few months after discontinuation (6 months).	TMP-SMX prophylaxis: 2113 AEs in 824 patients: 92 ADRs, the most common were: - Increased transaminases (n=25) - Azotemia (n=10) - Hyponatremia (n=9) - Leukopenia (n=9) 82 ADRs (89.1%) showed mild-to-moderate severity, and most did not require any intervention. 10 severe ADRs in 10 patients: six pancytopenias and one case of Stevens-Johnson syndrome. All severe ADRs resolved after discontinuation of TMP-SMX. NNH for 1 severe ADR was 101.

Trial	Number and Type of Patients	Combination therapies	Median Follow up	PJP and PJP-related outcomes	Adverse Reactions
Raso 2021[34]	67 patients: - Control (N=34; 51%). - Prophylaxis (N= 33; 49%) ITP patients	66% one prior treatment, 34% more than two before RTX: - corticosteroids 97% - IVIG 72% - splenectomy 15%	22 months	No incidence of PJP in any group.	No severe AEs due to prophylaxis. One patient interrupted TPM/SMX within the first week due to a skin reaction.
Catroux 2017[35]	93 patients: - Control (N=57; 61%) - Prophylaxis (N=36; 39%) TMP/SMX (n = 33), pentamidine (n = 2), atovaquone (n = 1) Autoimmune diseases	Concomitant/prior treatment: - Corticoids 83% - Azathioprine 31% - CYC 25% - MMF 15% - MTX 14% - Chemotherapy 11% - Cyclosporine 10% - Splenectomy 5% - TNF inhibitors 4% - Everolimus 1% - Anakinra 1%	25 months	- PJP incidence: 4% control *vs* 0% prophylaxis, NNT 25 N= 2 (not on prophylaxis or not in correct dosage or duration)- 1 case was severe. - Most infections (not only PJP) occurred less than 3 months after the first rituximab treatment. - ICU admission, mechanical ventilation and PJP mortality not reported.	Not reported
Hardak 2012[21]	132 patients: - Control (N= 99; 75%) - Prophylaxis (N=33; 25%) DLBCL patients	R-CHOP (6 cycles) + 2 courses of RTX (within 21 or 14 days- RCHOP-21 or RCHOP-14)	6 months	- PJP incidence: 5% control *vs* 0% prophylaxis, NNT 20 N= 5 control (1 patient in the R-CHOP-21, 4 in RCHOP-14). - No statistically significant risk factors were identified. - Median time for PJP: 76 days. - Mechanical ventilation: 20%. - ICU admission: not reported. - PJP mortality: 20% (1/5 with delayed diagnosis).	Not reported.
Lee 2021[33]	739 patients: - Control (N=602; 82%) - Prophylaxis (N=137; 18%) DLBCL patients	R-CHOP (3-8 cycles)	6.5 months	- PJP incidence: 8% control *vs* 0% prophylaxis, NNT 12.5 N= 49 control group. - Median time for PJP: 69 days. - ICU admission: 20%. - Mechanical ventilation: 18%. - PJP mortality: 16% (8/49). - Most PJP patients (91.9%) were over 50 years old.	AEs were only significant during PJP treatment, not during prophylaxis.
Faraji 2021[36]	494 patients: - Control (N=259; 52%) - Prophylaxis (N=235; 48%) Pemphigus patients	Prior treatment: - Prednisolone 100% - Azathioprine 28.3% - MMF 26.5% - MTX 13.6% - IVIg 1.6% - CYC 0.2% - Dapsone 0.2%. After rituximab: - methotrexate + prednisolone 1.4%	21 months	- PJP incidence: 0.4% control *vs* 0.4% prophylaxis: N= 1 control *vs* N=1 prophylaxis, NNT incalculable (no risk reduction) - ICU admission: 50%. - Mechanical ventilation: not reported. - PJP mortality: 0%. - Prophylaxis patient: PJP in the second cycle. Despite treatment, PJP developed again after the third cycle. - Control patient – time for PJP 60 days, ICU for 2 weeks.	Only one AE (generalized erythema and pruritus) during PJP treatment, not during prophylaxis. Improved with discontinuation of the drug.

Trial	Number and Type of Patients	Combination therapies	Median Follow up	PJP and PJP-related outcomes	Adverse Reactions
Hsu 2023[33]	148 patients: - Control (N=35; 24%) - Prophylaxis (N=113; 76%) Pemphigus patients	Concomitant/prior treatment: - Prednisolone 97.3% - Azathioprine 52.0% - Hydroxychloroquine 8.1% - Colchicine 6.6% - MTX 6.1% - Cyclosporin 2.7% - Minocycline 1.4% - Tacrolimus 1.4% - Sulfasalazine, 1.4% - MMF 1.4% - IVIg 0.7% - Levamisole 0.7% - CYC 0.7%	1 year	- PJP incidence: 2.0% control *vs* 0% prophylaxis: N= 3 control group. NNT 50 - Risk factor for PJP: Higher cumulative prednisolone dose (p=0.048). - PJP mortality: 0%. - Median time for PJP, ICU admission and mechanical ventilation not reported. - Despite being treated with higher dose of concomitant corticosteroids (p = 0.0001), the prophylaxis group had lower incidence of PJP.	3 patients experienced TMP/SMX related AEs. None were life-threatening events and all of them spontaneously resolved after discontinuation of TMP/SMX.
Park 2023[31]	818 patients: - Control (N=399; 49%) - Prophylaxis (N=419; 51%) Rheumatic patients	Concomitant treatment: High dose glucocorticoids 44.3% Prior treatment: - Azathioprine 13.0% - MTX 12.3% - MMF 9.3% - Cyclosporin 9.2% - Tacrolimus 7.9% - CYC 6.4%	1 year	- PJP incidence: 0.86% control *vs* 0.5% prophylaxis: N=7 control *vs* N=4 prophylaxis (all with reduced exposure). - Risk factor for PJP (in 10/11): High-dose steroids. - Median time for PJP: 86 days (prophylaxis- 124 days *vs* control-65 days) - ICU admission: not reported. - Mechanical ventilation: 91%. - PJP mortality: 64% (7/11). - NNT global: 146 (20 if risk factors *vs* 250 without risk factors) - Prophylaxis had no impact in PJP incidence in the subgroup not receiving high-dose steroids. (HR 0.63 [95% CI 0.0004-11.86])	TMP-SMX prophylaxis: 303 AEs. Only 12 ADRs: -Thrombocytopenia (N=3) - Increased AST/ALT (N=3) - Leukopenia (N=2) - Hyponatremia (N=2) - Azotemia (N=1) - Pancytopenia (N=1) Two were severe ADRs: Pancytopenia and an AST/ALT increase: both improved shortly after discontinuation of TMP/SMX. NNH for 1 severe AE was 86.

*RCHOP regime consists of 375 mg/m^2 rituximab, 750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, and 2 mg vincristine on day 1, as well as 100 mg prednisone on days 1–5, NNT- number needed to treat, AE-adverse event, ADR- adverse drug reaction, IVIG- intravenous immunoglobulin, ITP- immune thrombocytopenia, DLBCL- diffuse large B cell lymphoma, MMF- mycophenolate mofetil, MTX- methotrexate, CYC- cyclophosphamide, ICU- intensive care unit.

Primary Outcome

All patients in the prophylaxis group received TMP/SMX for prophylaxis, except three patients: pentamidine (n = 2), atovaquone (n = 1).

In the prophylaxis arm (n=2007), 17 (0.3%) PJP infections occurred, whereas in the control arm (n=4041), 147 (2.4%) infections were observed (OR, 0.35; 95% CI, 0.19-0.64) (Fig. 2 and Table 3). The NNT to prevent 1 episode of PJP was 36 patients (CER, 3.6%). No significant heterogeneity was observed in this comparison (I^2 = 0%; p = 0.48).

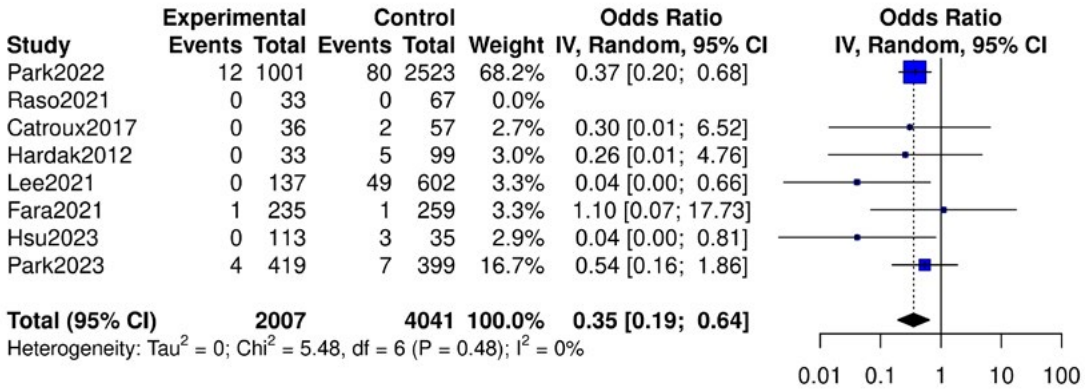

Figure 2. Incidence of PJP in prophylaxis *versus* no prophylaxis group (forest plot).

Table 3. Aggregated results simplified

	Prophylaxis	Controls
N	2007	4041
PJP incidence	0.3% (N=17)	2.4% (N=147)
PJP-related mortality	41% (N=7)	23% (N=34)
NNT	36	

PJP- *Pneumocystis jiroveci* pneumonia, NNT- number needed to treat

Secondary Outcomes

One hundred sixty-four PJP infections occurred, with a mortality rate of 25.0% (N=41). One study was also responsible for the majority of the ADRs – 92 events (out of 104 total) with an incidence of 18.1 per 100 person-years.[30] The Park studies were the only to report severe ADRs (n=12) and the number needed to harm (NNH) was 86-101.[30] Pancytopenia was most common (n= 6) and only one case of Stevens-Johnson syndrome occurred. All severe ADRs resolved after discontinuation of TMP-SMX.

In one study, the authors opted to report all AEs (adverse events), irrespective of correlation with therapy.[31] For this reason, a large proportion of AEs were not caused by the prophylaxis (74% unrelated (224/303)). AEs were also highly reported in the control group (220/399, 55%), as SAEs (severe AEs) – incidence 9.5%. This author's conservative approach was due to the risk of overestimating the safety profile based on only ADRs.

Therefore, calculating the total NNH in our meta-analysis was not possible due to only having access to aggregated and not individual data and different evaluated events (AEs and ADRs).

DISCUSSION

Our analysis showed us a difference in the PJP incidence between the prophylaxis and the control group, 0.3% *vs* 2.4%, respectively, what seems to support prophylaxis. When looking specifically into each study, we can see that the prophylaxis group showed smaller PJP incidences in 6 of the 8 studies and in 4 of these, the incidence in the prophylaxis group was 0%. Once again, all these data points to a beneficial effect of the prophylaxis.

Despite that, our analysis is prone to some confounding bias due to the retrospective nature of the studies, variations in PJP diagnostic criteria and different diseases and immunosuppressive regimens.

Throughout our analysis, we found no data regarding the prophylaxis effect of TMP- SMX in glomerular diseases, in light of previous reports.[7] PJP risk in rituximab monotherapy, our main goal, was also difficult to access since all studies involved combined immunosuppressant schemes. The most common adjuvant therapies were corticosteroids, used in 6 of the 8 studies. Other adjuvants were chemotherapy agents (cyclophosphamide, doxorubicin, and vincristine), classic immunosuppressive agents (such as azathioprine and MMF), and immunoglobulins.

Rituximab indications were also varied and the studies we analyzed included hematologic, rheumatic, oncologic, transplant and dermatologic patients. This fact brings a lot of heterogeneity to the studied populations, which can cause biases in the data analysis. Some patients might be more susceptible to infectious diseases like PJP than others, based only on the physiopathology of the different underlying entities. This might mean that some of these diseases have a bigger need for prophylaxis than others or related to adjunctive therapy. NNT varied between diagnoses and within the same diagnosis in different

studies: rheumatic disease 23-146, hematologic disease 13-36 (no risk reduction for immune thrombocytopenia and R-CHOP patients NNT 13-20), solid organ transplant group 27, pemphigus (varied from no risk reduction to NNT 50).[21,30-36] Hematologic patients seem to be at higher risk, especially for R-CHOP patients, dermatologic patients at lower risk and rheumatic disease with more varied outcomes. Adjunctive therapy seems to be more important than basal diagnosis. High cumulative corticosteroid dose was the most common and the most relevant risk factor. It conditioned a NNT of 17 against 46 for the remaining patients in Park *et al* (2022) and a NNT of 20 *vs* 250 for patients without risk factors in Park *et al* (2023).[30,31] It was also mentioned as a major risk factor in Hsu *et al* (2023).[32] Another identified risk factor was azotaemia, in Park *et al* (2022).[30] The remaining probable risk factors, like age did not show any statistical relevance.

One of the studies, Park *et al* (2022) weighted 68% to the outcome analysis and it contributed to the statistical significance of the results.[30] To increase the N the authors decided to include hematologic, rheumatic and pre/post-solid organ transplantation patients. Multivariable analysis identified azotemia (adjusted subdistribution hazard ratio [aSHR], 2.38) and concomitant treatment with high-dose steroids (aSHR, 3.09) as the two most important factors that increase the risk of PJP. These factors are superimposed on the patients' group.

Median time for PJP development was similar between studies, from 69 to 86 days.[21,30,33] In Park *et al* (2023), the authors verified that the median time for PJP differed significantly between the prophylaxis and the control group, from 124 days to 65 days, respectively.[31] This fact enlightens that TMP-SMX, besides reducing PJP incidence, can also delay the development of the infection.

Only 4 studies reported ICU admission and mechanical ventilation rates. In Park *et al* (2022), the ICU admission rate between PJP patients was 35%, with most of the cases being from the control group (78%), and the need for mechanical ventilation rate was 30%, once again based mostly on control patients (75%).[30] In Hardak *et al* (2012) and Lee *et al* (2021) the mechanical ventilation rate was 20% and 18%, respectively.[21,33] Also in Lee *et al* (2021), the ICU admission rate was 20%.[33] All patients were from the control group. At last, in Park *et al* (2023), there was a 91% rate of mechanical ventilation need, all in patients in the control group or in patients with a reduced exposure to prophylaxis.[31] Based on this data, the PJP prophylaxis seems to reduce the severity of the infection, since it correlates with a lower need for ICU admission and mechanical ventilation support.

In our revision, the percentage of PJP incidence in the control groups was low (0% to 8%), but mortality was higher (globally in our analysis 25% but varied between studies from 0% to 64%). AEs and ADRs were difficult to calculate due to different methods reporting them, but all resolved with therapy cessation and correlated with dosage (more frequent during treatment when compared with prophylaxis).

CONCLUSION

From our analysis, prophylaxis with TMP-SMX is justifiable in patients with combined therapies with rituximab. On the other hand, in rituximab monotherapy data is not as robust, and as there is no recommendation, the decision should be patient-based. The optimal duration of prophylaxis it is also unclear since PJP risk increases after prophylaxis suspension. This represents a significant clinical gap that could impact long-term patient management.

To clarify all the unknown data and to establish strong and evidence-based recommendations, more studies should be held, ideally randomized controlled trials.

Awards and Previous Presentations

Manuscript based on an academic thesis: *Pneumocystis jiroveci* prophylaxis in non-HIV patients treated with rituximab, 2023, Faculdade de Medicina da Universidade de Lisboa.

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Contributorship Statement

MLG: Collected the data, draft and elaboration.

IG: Collected the data, statistical analysis and interpretation.

JG: Provided significant intellectual content and contributed to revision of the manuscript.

JAL: Responsible for study conception and contributed to revision of the manuscript.

All authors approved the final version to be published.

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