Rate of infections in severe necrotising vasculitis patients treated with cyclophosphamide induction therapy: a meta-analysis

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ABSTRACT

Objective. *Infections are common complications of necrotising vasculitis. We aimed to determine the rate of infections in patients with severe necrotising vasculitis treated with cyclophosphamide (CYC) combined with high dose glucocorticoids (GC).*

Methods. *Searches of MEDLINE, Embase and Cochrane Library databases (1990 to May 2016) were performed. Inclusion criteria were randomised controlled trials of intravenous (IV) or oral (PO) CYC induction therapy for granulomatosis and polyangiitis (GPA), microscopic poyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), and systemic polyarteritis nodosa (PAN). Pooled rates of infectious complications were determined by random effects meta-analyses. Meta-regression was performed to identify variables associated with severe infection.*

Results. *Search results yielded 2636 references; 14 studies with a total of 888 subjects met inclusion criteria. The mean age of participants ranged from 39 to 75 years. Mean cumulative doses of CYC were 2.7 to 50.4 g and of GC were 6 to 13 g. The pooled rate per year per gram of CYC of severe infection was 2.2% (95% CI: 0.9, 5.3%, I^2 =58.7%), any infection was 5.6% (95% CI: 1.8, 16.7%, I^2 = 79.1%) and infection-related deaths was 1.7% (95% CI: 0.8, 3.9%, I^2 = 0%). By meta-regression, age, creatinine and cumulative GC dose were not significantly associated with the rate of severe infections.*

Conclusion. *The rate of severe infections and infection related mortality in patients with severe necrotising vasculitis treated with CYC + GC induction therapy is high.*

Introduction

Necrotising small-vessel vasculitis includes polyarteritis nodosa (PAN) and antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis (AAV). There are three major types of AAV: granulomatosis with polyangiitis (GPA; formerly known as Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg-Strauss syndrome) (1-3). The combination of CYC and GC as an induction therapy has significantly improved the survival of patients with severe necrotising vasculitis (2-4). Survival of patients with generalised vasculitis using CYC for 3 to 6 months with high dose GC, followed by low-dose azathioprine and low-dose glucocorticoid is now greater than 90% after 18 months follow-up (3). The likelihood of survival after 5 years from the initial episode of ANCA-associated vasculitis is more than 80% (5).

Despite its efficacy in improving the overall survival of the patients with severe necrotising vasculitis, treatment of severe necrotising vasculitis with CYC is complicated by drug toxicity. Studies of patients enrolled in multiple clinical trials have demonstrated that infection is the greatest threat to patients with severe necrotising vasculitis in the first year of treatment. In two retrospective studies analysing over 100 patients with ANCA-associated vasculitis treated with CYC and GC, 48-50% of all deaths in the first year of follow-up were attributable to infection (6, 7). Rituximab (RTX) has been shown to be non-inferior to CYC for induction of remission in AAV in two trials; however, it appears to have a similar risk of infection compared to CYC (8, 9). Furthermore, access to RTX remains limited in many countries. Therefore, CYC continues to be frequently used for the treatment of AAV. To optimise therapy for patients with AAV and other forms of severe necrotising vasculitis, it is imperative to understand the risks of the CYC induction therapy, in

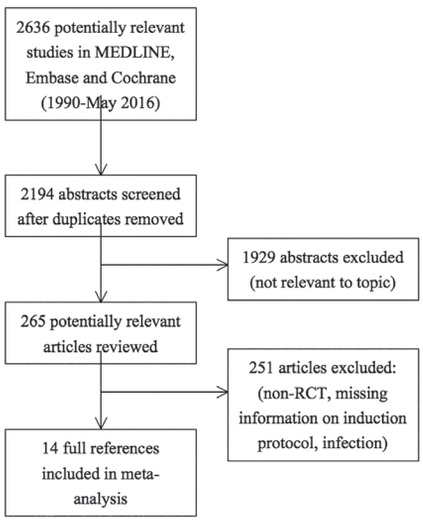

Fig. 1. Search results. Studies identified from the literature search with reasons for exclusion.

particular infection, which is the leading threat for mortality in the first-year of treatment (6, 7). This study aims to review the literature in order to quantify the rate of infection of induction therapy with CYC combined with GC for the treatment of severe necrotising vasculitis.

Methods

Literature search

We performed a literature search using the MEDLINE, Embase and Cochrane Library databases. Search dates were from 1990 up to and including May 2016. Our search strategy combined terms for 'anti-neutrophil cytoplasmic antibody associated vasculitis', 'granulomatosis with polyangiitis (Wegner's granulomatosis)', 'microscopic polyangiitis', 'eosinophilic granulomatosis with polyangiitis (Churg Strauss syndrome)', and 'cyclophosphamide (Cytoxan)' (Supplementary Table 1).

Study selection

Inclusion criteria were: (i) English language, (ii) full-text articles of randomised controlled trials of induction therapy for new or relapsing AAV with CYC + GC, (iii) patients satisfying the 1994 Chapel-Hill or ACR criteria for GPA, MPA or EGPA (10-12), (iv) provision of data on the infectious complications during the study period or follow-up, and (v) provision of the cumulative dosage of CYC and GC during the induction phase or inclusion of their CYC and GC induction protocol so that a cumulative dosage could be estimated. Trials that enrolled patients with systemic PAN not secondary to hepatitis B infection were included if they also included patients with AAV. Studies of cutaneous PAN were excluded. Two independent reviewers (MJ and LB) selected papers by title and abstract. Hand searches of the references in relevant papers were conducted to identify any additional articles. Two independent reviewers (MJ and LB) subsequently reviewed the full text articles.

Data extraction, effect measure and quality appraisal

From the included articles, we extracted information including number of participants, patient characteristics, intervention medications and doses, mean duration of follow-up, number, type and severity of infections as reported by the authors. There was no uniform definition of a severe infection in the trials included in this meta-analysis and some authors did not report how severity was defined. When reported, severity of infection was defined based on risk of death and association with hospitalisation, use of intravenous antibiotics, irreversible damage, oras per the common terminology criteria for adverse events, proposed by the US Department of Health and Human Services, National Institutes of Health, and National Cancer Institute (13). If the included trials only reported the median values, they were converted to the mean assuming normal distribution. Creatinine was converted from mg/dL to μmol/L using www.endmemo.com. If not reported in studies, the cumulative dose of CYC and GC was estimated using the induction protocols provided by the authors. The risk of bias in the RCTs was analysed using the Cochrane Collaboration's tool (14). Publication bias was assessed using Funnel plots.

Statistical analysis

Meta-analyses using the DerSimonian and Laird method were performed to estimate the rates of infectious complications (severe infections, any infection or infections causing death) in AAV patients treated with CYC + GC induction therapy. Severe infections were defined as those (i) resulting in death, or (ii) requiring hospitalisation or IV antimicrobial therapy, or (iii) being reported as severe by the authors. Given that the CYC dosing and duration of follow-up varied widely across studies, the % of patients with infectious complications per year per gram of cyclophosphamide was reported. Heterogeneity of the included studies was reported with the I^2-statistic. Meta-regression was performed using the method of moments for the following variables selected *a priori*: age, serum creatinine level and cumulative dose of GC. The following subgroup analyses were performed *post-hoc:* infection rates for the different types of vasculitis and for publication year (prior to 2000, 2000-2010 and after 2010). All statistical analyses were performed using Comprehensive Meta-Analysis v. 2 software.

Results

The literature search identified 2,636 citations with 14 studies meeting inclusion criteria. Reasons for exclusion are shown in Figure 1. Characteristics of the included studies are shown in Table I (8, 9, 15-26). The mean follow-up period ranged from 0.5–5.0 years. The mean age of patients ranged from 39-75 years. Cumulative CYC dose per person ranged from 6.5–27.8 g for patients treated with intravenous (IV) CYC, and 11.5–50.4 g for those treated with oral (PO) CYC. In three studies (Adu *et al*., Jones *et al*., Stone *et al*.), patients' induction treatment was followed by azathioprine (8, 9, 15). Eight studies had a low risk of bias (Table I). The remaining 6 studies had evidence of high publication bias as they were open-label trials or had incomplete outcome data (Supplementary Table II).

In AAV patients treated with CYC + GC, the pooled rate (per year per gram of CYC) of severe infection was 2.2% (95% CI: 0.9, 5.3%, I^2=58.7%) (Fig. 2), any infection was 5.6% (95% CI: 1.8, 16.7%, I^2=79.1%) (Fig. 3) and infection-related deaths was 1.7% (95% CI: 0.8, 3.9%, I^2=0%) (Fig. 4). The risks of any infection, severe infection, and death by infection were analysed for studies that included GPA and/or MPA

Table I. Characteristics of randomised clinical trials included in the meta-analysis.

Studies	Induction Treatment	Disease (%)	Number of participants	Baseline BVAS	Mean follow-up (years)	Mean age at enrolment (years)	Baseline Mean Cr (µmol/L)	PJP prophylaxis	Cumulative CYC dose per person (IV vs. PO) (g)	Cumulative GC dose per person (g)	Risk of Bias
Adu *et al*. 1997 (15)	IV CYC vs PO CYC	PAN (14.8),. MPA (31.5), GPA (53.7)	24 (IV) 30 (PO)	NR	2.8 (IV) 3.0 (PO)	50	139 (IV) 234 (PO)	NR	6.5 (IV) 11.5 (PO)	12.5 (IV) 7.8 (PO)	Low
Cohen *et al*. 2007 (16)	IV CYC (6 pulses) vs. IV CYC (12 pulses)	EGPA (100)	23 (6 IV pulses) 25 (12 IV pulses)	26.1	4	52	100	WBC<300/mm^3	19.6 (IV)	6.0	Low
De Groot *et al*. 2005 (17)	PO CYC vs. PO MTX	GPA (93.7), MPA (6.3)	49 (CYC) 51 (MTX)	15	1.5	52	90	Optional	37.7 (PO)	6.4	Low
De Groot *et al*. 2009 (18)	IV CYC vs. PO CYC	GPA (37.6), MPA (47.7), RV (14.8)	76 (IV) 73 (PO)	20 (IV) 21 (PO)	1.5	57 (IV) 58 (PO)	225 (IV) 222 (PO)	Suggested	8.9 (IV) 16.2 (PO)	7.6 (IV) 7.6 (PO)	High
Gayraud *et al*. 1997 (19)	IV CYC vs. PO CYC	PAN (68.0), EGPA (32.0)	13 (IV) 12 (PO)	NR	5.1	39 (IV) 47 (PO)	NR	NR	13.1 (IV) 50.4 (PO)	6.7 (IV) 6.7 (PO)	High
Guillevin *et al*. 1995 (20)	IV CYC vs. IV CYC + PE	PAN (77.4), EGPA (22.6)	34 (CYC) 28 (CYC + PE)	NR	5	60 (CYC) 57 (CYC + PE)	143.2	WBC<300/mm^3	13.1 (IV)	10.8	Low
Guillevin *et al*. 1997 (21)	IV CYC vs. PO CYC	GPA (100)	27 (IV) 23 (PO)	NR	2.6 (IV) 2.1 (PO)	54 (IV) 53 (PO)	252 (IV) 182 (PO)	Yes	27.8 (IV) 43.9 (PO)	12.9	Low
Guillevin *et al*. 2003 (22)	IV CYC (6 pulses) vs. IV CYC (12 pulses)	MPA (72.3), PAN (27.7)	31 (6 IV) 34 (12 IV)	21.8	2.7	55	213	Yes	27.0 (IV)	6.1	Low
Haubitz *et al*. 1998 (23)	IV CYC vs. PO CYC	GPA (46.8), MPA (53.2)	22 (IV) 25 (PO)	NR	3.6 (IV) 3.1 (PO)	NR	329 (IV) 245 (PO)	No	16.4 (IV) 38.4 (PO)	2.6	High
Jayne *et al*. 2007 (24)	PO CYC vs. PO CYC + PE	GPA (30.7), MPA (69.3)	67 (CYC) 70 (CYC + PE)	21	1	60	734	Suggested	22.1 (PO)	8.9	Low
Jones *et al*. 2010 (8)	IV CYC vs. RTX	GPA (50.0), MPA (36.4), RV (13.6)	11 (CYC) 33 (RTX)	19 (CYC)	1	67	NR (given as eGFR)	Suggested	5.6 (IV)	2.1	High
Pagnoux *et al*. 2015 (26)	IV CYC low dose vs. IV CYC high dose	GPA (34.6), MPA (42.3), PAN (9.6), EGPA (13.5)	53 (low CYC) 51 (high CYC)	NR	3	75	234	Yes	2.7 (IV low) 5.6 (IV high)	9.6	High
Ribi *et al*. 2010 (25)	IV/PO CYC vs. AZA	MPA (53.2), PAN (46.8)	19 (CYC) 20 (AZA)	12.6	5.2	57	82	WBC<300/mm^3	6.5 (IV/PO)	NR	High
Stone *et al*. 2010 (9)	PO CYC vs. RTX	GPA (75.1), MPA (24.4), Uncertain (0.5)	98 (CYC) 99 (RTX)	8.2	0.5	52	NR (given as CrCl)	Yes	25.2 (PO)	6.4	Low

Values are for CYC groups.
CYC: cyclophosphamide; GC: glucocorticoid; IV: intravenous; PO: oral; PE: plasma exchange; NR: not reported, RV: renal limited vasculitis.

only separately from studies that included PAN; there was no significant difference between them (Supplementary Table III). There was no difference in the rate of severe infection based on the publication date (data not shown). Details regarding the types of infections were not provided by all studies; most of the severe infections were pneumonias or sepsis. Respiratory infection rate was only reported in nine studies (Supplementary Table IV).

Ten studies reported the use of prophylactic antimicrobials for *Pneumocystis jiroveci*. Vaccination history was not reported. When accounting for cumulative dose, there was no significant difference in infection rate for oral *versus* intravenous CYC. Also, no significant association was found between severe infection rate and increasing cumulative doses of GC, age and creatinine: β=0.04271, p=0.12637, β=-0.00126, p=0.34935 and β=0.00047, p=0.55189, respectively. The effect of disease activity on infection rate could not be determined as the Birmingham Vasculitis Score was inconsistently reported in the included studies. The funnel plots for severe infection, any infection, and infection-related deaths revealed significant publication bias (Supplementary Fig. 1).

Discussion

This meta-analysis estimated the rate of infectious complications related to CYC induction treatment for severe necrotising vasculitis. It has been reported that infection is the leading cause of death during the first year of therapy (6). Despite its significance, the reported rates of infections in clinical trials and observational studies vary widely (4, 5, 10-24). A major contributor to the variability in studies is variations in the CYC cumulative dose. Given the significant variability in cumulative CYC dose across studies, we chose to report the infection rate per gram of CYC exposure over time.

Our meta-analysis estimated the risk of severe infection at 2.2%, any infection at 5.6% and infection-related deaths at 1.7% per year per gram of CYC. This quantification is relevant for clinicians when discussing the benefits and

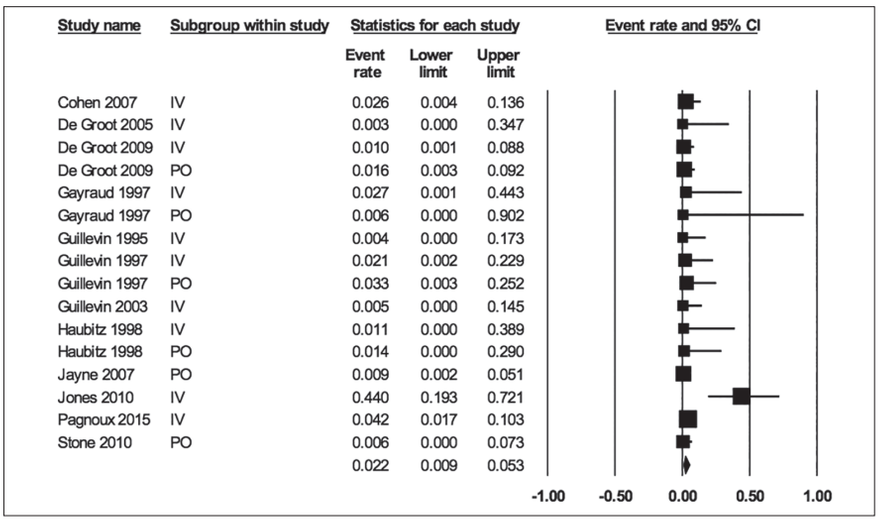

Fig. 2. Rate of severe infections. Forest plot of severe infection rate for patients with AAV treated with CYC + GC induction therapy. Effect size is the proportion of patients with severe infection per gram of CYC per year and 95% confidence intervals.

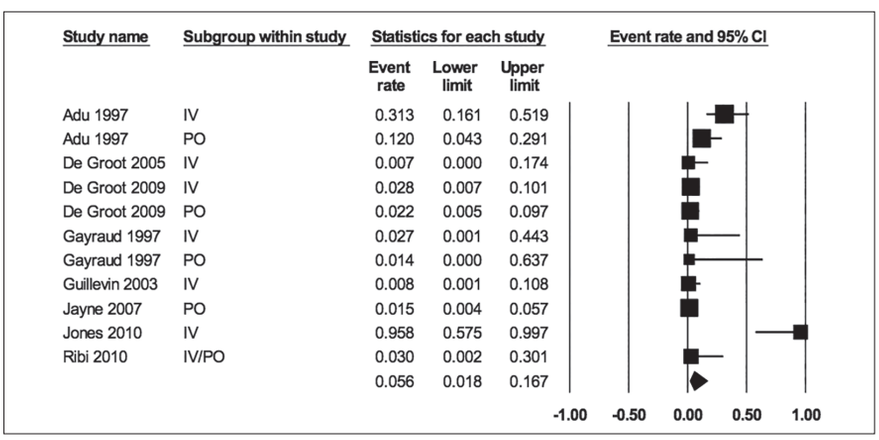

Fig. 3. Rate of any infection. Forest plot of any infection rate for patients with AAV treated with CYC + GC induction therapy. Effect size is the proportion of patients with severe infection per gram of CYC per year and 95% confidence intervals.

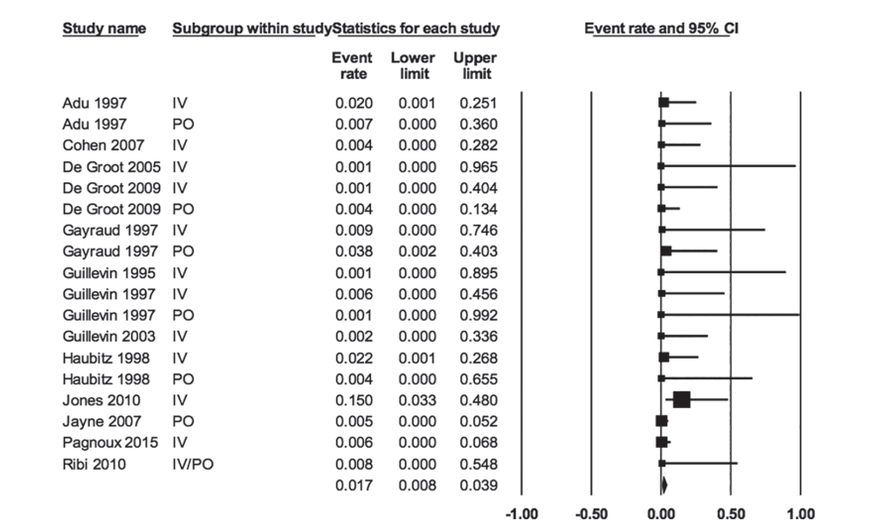

Fig. 4. Rate of death due to infection. Forest plot of death due to infection rate for patients with AAV treated with CYC + GC induction therapy. Effect size is the proportion of patients with severe infection per gram of CYC per year and 95% confidence intervals.

potential side effects of an induction therapy with CYC with patients. Randomised controlled trials investigating oral CYC, which has a higher cumulative CYC dose compared to IV CYC showed lower infection rates in the IV CYC groups (13, 16). The current European League Against Rheumatism (EULAR) and Canadian recommendations for the management of AAV support minimising CYC exposure to reduce adverse events (25,26). These recommendations suggest CYC induction regimens based on the de Groot *et al*. trial (CYCLOPS): 15 mg/kg of CYC every 2 weeks x 3 and then every 3 weeks for a total of 6 infusions, or for 3 months after achieving remission (18, 29, 30). Considering dose adjustment based on renal function and age, cumulative CYC doses for induction therapy based on these guidelines ranges from 3 to 10 g. This is considerably lower than CYC induction regimens used in earlier studies. Even with these reduced cumulative CYC doses, our review reveals that the rate of serious infections is very high at 7.2–24% per year.

Various risk factors for infection in AAV patients have been reported in the literature, including cumulative GC dose, impaired renal function, higher disease activity, older age, and lack of prophylaxis for Pneumocystis jiroveci Pneumonia (PJP) (8, 21, 24, 31, 32). Using meta-regression, we did not find a significant association between severe infection rate and cumulative GC dose, increasing creatinine or increasing age. However, with the imprecise effect sizes, we were underpowered to detect a difference and could not account for potential confounders. In addition, the average age of participants in all but two of the included studies was less than 65 years old. Jones *et al*. (RITUXVAS) included older patients with significant renal disease and reported a higher rate of severe infections (8). Pagnoux *et al*. specifically investigated complication rates in older AAV patients; infection rates in this study were higher in patients with higher cumulative CYC and GC doses (22). Studies inconsistently reported disease activity. Therefore, we did not include it in the analysis.

PJP prophylaxis is recommended in patients with GPA that receive CYC and daily GC therapy (30, 33). A hospital registry study reported the frequency of PJP to be 89 cases/10,000 hospitalisations/year in patients with GPA over a 12-year period (34). In Guillevin *et al*., the induction protocol involving CYC and GC was revised to include trimethoprim sulfamethoxazole 400 mg/day as prophylaxis given the high frequency of PCP in the first 12 patients recruited (21). However, implementation of PJP prophylaxis was not consistent across other induction remission trials, which reflects a varied local practice. Vaccination use was not reported in studies and may also have contributed to variability in infection rates. Treatment with rituximab as an alternative to CYC for induction therapy for AAV has not been shown to reduce infection risk. In the RAVE trial, 7% of patients had ≥ grade 3 infections in the RTX and CYC-treated patients during the first six months, increasing to 12% in the RTX and 11% in the CYC-treated group after 18 months. There is a lack of data for the management of patients that have concomitant significant infection and severe necrotising vasculitis requiring induction therapy. Potential options for these challenging cases are IVIG and plasma exchange until infection is controlled with antimicrobials prior to using standard induction therapies (30). There are several limitations of this meta-analysis. The first is the heterogeneity observed among studies, which may be attributed to the differences in the induction protocol and use of infection prophylaxis. Other potential sources of heterogeneity include differences in organ involvement, disease duration, numbers of patients with relapsing *vs*. new-onset disease, exposures to other immunosuppressants, co-morbidities that predispose to infection and study population differences (type of vasculitis, genetics, and environmental exposures, including geographic variations in endemic infections). Systemic PAN not due to hepatitis B infection was included in several trials. This likely reflects the 1990 American College of Rheumatology classification criteria that defined PAN and MPA together (35). Studies that included PAN did not report results separately from the other types of vasculitis, so we were not able to analyse them separately. However, the risks of any infection, severe infection, and death by infection in studies that included PAN did not differ significantly from the studies that included GPA and/or MPA only (Supplementary Table III). Inclusion of studies with a long duration of follow-up may have led to an underestimation of the infection rate as the risk of infection has been reported to be highest early in the course of the induction therapy (6, 7). Another limitation of the meta-analysis is the lack of a standardised definition for infection severity in the included studies with the exception of the RAVE trial, which used the common terminology criteria for adverse events (13).

In conclusion, the rate of severe infections is high in AAV patients undergoing CYC + GC induction therapy: 2.2% per gram of CYC per year. Quantifying the risk assists physicians in managing and counselling these patients. The Canadian Rheumatology Association recommends adjusting the dosage of CYC based on the characteristics of patients (30). Yet, infection remains a significant complication. The use of rituximab as an alternative induction therapy has not been shown to decrease infection rate compared to CYC induction (8, 9). Other measures to prevent infection, such as decreasing corticosteroid doses, using infection prophylaxis and other emerging therapies may improve outcomes in these patients.

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