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Outcomes and compliance with standards of care in ANCA-associated vasculitis – insights from a large multi-region audit

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Short title: Standards and outcomes of routine care in ANCA-associated vasculitis

Abstract

Objectives: We aimed to conduct a large audit of routine care for patients with ANCA-associated vasculitis (AAV).

Methods: We invited all 34 hospitals within one health region in England to undertake a retrospective case note audit of all patients newly-diagnosed or treated with Cyclophosphamide or Rituximab for AAV April 2013-December 2014. We compared clinical practice to the BSR guideline for the management of adults with AAV, and use of Rituximab to the NHS England commissioning policy and NICE Technology Appraisal.

Results: We received data from 213 patients. Among 130 newly diagnosed patients, delay from admission to diagnosis ranged from 0-53 days (median 6, IQR 3-10.5) for those diagnosed as in-patients. BVAS score was recorded in 8% at diagnosis. Remission at 6 months was achieved in 83% of patients. 1-year survival was 91.5%. 130 patients received Cyclophosphamide for new-diagnosis or relapse. The correct dose of i.v. cyclophosphamide (within 100mg of the target dose calculated for age, weight and creatinine) was administered in 58%. 25% of patients had an infection requiring hospital admission during or within 6 months of completing their cyclophosphamide therapy. 76 patients received Rituximab for new-diagnosis or relapse. 97% patients met NHS England or NICE eligibility criteria. PJP prophylaxis (recommended in the summary of product characteristics) was given in only 65% of patients.

Conclusion: We identified opportunities to improve care, including compliance with safety standards for delivery of cyclophosphamide. Development of a national treatment protocol / checklist to reduce this heterogeneity in care should be considered as a priority.

Key words: ANCA-associated vasculitis, Audit, Routine care, Cyclophosphamide, Survival

Key messages:

1. Infections requiring hospital admission occurred in 25% of ANCA-associated vasculitis patients receiving cyclophosphamide.
2. Only 58% of ANCA-associated vasculitis patients on i.v. cyclophosphamide received the correct dose (within a 10% tolerance).

3. Tertiary-referral centres treated ANCA-associated vasculitis sooner, and more patients received correct doses of cyclophosphamide

Introduction

ANCA-associated vasculitis (AAV) has high mortality, with the greatest mortality risk occurring within the first year after diagnosis. Yet there is very little data on the process and outcomes of routine NHS clinical care during this time period, aside from individual centre case series or small clinical trials. However, the patient charity Vasculitis UK frequently describes that their members report variations in clinical practice and outcomes throughout the UK.

Remission induction of AAV with cyclophosphamide is probably the most frequent non-cancer indication for cytotoxic chemotherapy. National guidance from the National Chemotherapy Advisory Group, designed to ensure quality and safety of all chemotherapy services, is also applicable to non-cancer chemotherapy [1]. The publication of BSR guidelines on the Management of adults with ANCA-associated vasculitis[2], and an NHS England commissioning policy for the use of Rituximab in AAV [3], followed by a NICE Technology Appraisal [4] provided further benchmarks against which to assess care.

The aim of this audit was to compare current practices, compliance with national guidelines and outcomes within a large, representative and geographically-defined area in England.

Methods

Rheumatology units in all 34 hospitals within one of the four health regions in England (Midlands and East - population 6,980,000) were invited to undertake a retrospective case note audit of all ANCA-associated vasculitis patients who were either newly diagnosed, or treated with Cyclophosphamide or Rituximab for relapse, during April 2013-December 2014. Each invitation recommended involving their hospital's nephrology unit. Patients were considered to have ANCA-associated vasculitis if this was their diagnosis given by a hospital physician. We developed and piloted a set of audit questions derived from the BSR guidelines, NHS England and NICE technology appraisal. We provided guidance on how to identify cases through departmental database, clinic letter, day-case and inpatient

admissions searches. Data were collected locally, and uploaded onto a web-based survey. Survey software was compliant with ISO 27001, the internationally recognised gold standard for information security systems, hosted by The Dudley Group NHS Foundation Trust clinical audit department. The form ensured complete data entry for most questions, as it could not submitted unless questions were answered. Data were collected on specialty of attending physician, place of diagnosis, dates of symptom onset, admission or first clinic appointment, and diagnosis, BVAS organ systems involved, details of remission induction, documentation of disease activity and damage, compliance with cyclophosphamide and rituximab safety standards, and outcomes including hospitalization for infection and death. Diagnostic delay was retrospectively estimated from information recorded in the medical notes, and was defined as the time from the date of the first reported symptom attributed to AAV to the date of diagnosis. Patient age, sex, subtype of AAV diagnosis, and ANCA-type were collected later, after completion of initial data entry. Tertiary-referral centres were defined as hospitals that at least 2 other hospitals reported that they made tertiary referrals to for ANCA-associated vasculitis. Tertiary-referral centres were compared to the other non-tertiary centres using chi-squared tests for categorical data, and Wilcoxon's rank sum test for continuous non-normally distributed data. 1 year survival was calculated using Kaplan-Meier methods. The odds ratio (OR) for infection was estimated using logistic regression, and the hazard ratio (HR) for death was estimated using cox regression; both were adjusted for confounders (age and renal involvement). Available case analysis was used where there were missing data. Statistical analyses were performed using Stata 14 statistical software (Statacorp, Texas, USA). This project was approved by the audit department of each trust that participated.

Results

We received data about 213 patients from 20 units: 130 newly diagnosed patients, and an additional 83 relapsing patients who were treated with cyclophosphamide or rituximab during the audit period. Between 1 and 41 patients were included by each unit. 144 (68%) were treated primarily by Rheumatology, and 69 (32%) by Nephrology.

Missing data: There were no missing data for audit outcomes. For the data collected at a later stage, there were some missing data (age (1%), sex (7%), diagnosis (10%) and ANCA-type (6%)).

New diagnosis

Baseline characteristics of the 130 newly diagnosed patients are shown in table 1. The median age was 67 (interquartile range 56-73), and 52 (43%) were female. 57 (49%) had granulomatosis with polyangiitis (GPA), 49 (42%) had microscopic polyangiitis (MPA) and 10 (9%) had eosinophilic granulomatosis with polyangiitis (EGPA). 72 (55%) were diagnosed as inpatients, and 58 (45%) as outpatients. Frequency of organ involvement at diagnosis is shown in table 2. Diagnostic delay from first symptoms to diagnosis was median 2.6 (interquartile range 1.2-6.1) months. It was shorter in those diagnosed as inpatients (1.8, 95% CI 0.9-3.7) compared to outpatients (4.1, 95% CI 2.0-12.6). Among inpatients, delay from admission to diagnosis ranged from 0-53 days (median 6, IQR 3-10.5). BVAS score was recorded in 10/130 (8%) at diagnosis and 8/121 (7%) at 6 months. The first choice of agent for remission induction was Cyclophosphamide (CYC) in 99 (76%), Rituximab in 6 (5%), and other agents in 25 (19%). Prednisolone dose at treatment initiation was median 55mg, (IQR 40-60mg, range 0-100mg) and additional i.v. methylprednisolone was administered in 60 (46%). At 6 months the prednisolone dose was median 9.5mg (IQR 5-10mg, range 0-60mg) among the patients documented to be in remission. Remission at 6 months was achieved in 101 (83%) of patients. 1-year survival was 90.8%. In the 76 patients who were recorded as having renal involvement, 1-year survival was 85.5%.

Of the 99 newly diagnosed patients treated with CYC, 74 (75%) received i.v. and 25 (25%) oral. 24 (24%) had infections requiring hospitalisation during or within 6 months of CYC treatment. One-year survival in this subgroup was 87.9%. Compared to i.v., the crude OR for infection with oral CYC was 2.2 (0.8-6.0) and HR for death was 2.3 (0.8-6.6). Once adjusted for age and renal involvement, OR for infection remained elevated at 1.8 (0.6-5.1) and HR for death was 1.7 (0.5-5.3) (table 2)

Cyclophosphamide safety standards[1,2]

130 patients received Cyclophosphamide for new-diagnosis or relapse: 101 (78%) received i.v. and 29 (22%) received oral (table 3). The correct dose of i.v. cyclophosphamide could be calculated for 95 (94%) of these based on BSR recommendations for age, weight and renal function, within a tolerance of +/- 100mg, based on the dose-banding for cancer chemotherapy introduced by NHS England which uses dose-bands within 5-10% of target dose[5]. The correct dose was administered in only 50 (58%), with under-dosing in 32 (34%) and over-dosing in 13 (8%). 1000mg was the most common dose given to those who received an un-recommended dose, and those who were under-dosed were on average younger and heavier, and those who were over-dosed were on average older and lighter than the whole cohort. At least one FBC was checked 7-10 days after the first dose of p.o. or i.v. cyclophosphamide in 119 (92%) patients. The total cumulative cyclophosphamide dose per patient was median 6g, interquartile range 4-9g, range 0.1-21g. No patients exceeded a lifetime exposure of 25g. Mesna was given in 99 (76%) of patients. PJP prophylaxis was given in 106 (82%) of patients. 33 (25%) patients had an infection requiring hospital admission during or within 6 months of completing their cyclophosphamide therapy.

Rituximab safety standards, and compliance with NICE / NHS E criteria for eligibility[3,4]

76 patients received Rituximab for new-diagnosis or relapse (table 4). The dosing schedule among the 16 patients newly diagnosed was 1g x2 in 15 (94%), and 375mg/m2 x4 in 1 (6%). The dosing schedule among the 60 patients treated for relapse was 1g x2 in 35 (58%), 375mg/m2 x4 in 16 (27%), and 1g x1 in 7 (12%). 74 (97%) patients met NHS England or NICE eligibility criteria. Pneumocystis jiroveci pneumonia (PJP) prophylaxis (recommended in the summary of product characteristics (SPC)) was given in only 49 (65%) of patients. Immunoglobulins were checked prior to Rituximab in 63/68 (93%) patients.

Tertiary and non-tertiary referral centres

Of the 130 newly diagnosed patients, 45 (35%) were treated in four tertiary-referral centres, and 85 (65%) were treated in 16 non-tertiary centres (table 5). Delay between admission and diagnosis was median 4, IQR 2-13 days in tertiary-referral centres, compared to median 7, IQR 4-11 in non-tertiary centres

(p=0.4). Delay between diagnosis and starting immunosuppression was median 4, IQR 3-10 days in tertiary-referral centres, and median 9, IQR 3-19 in non-tertiary centres (p=0.01). Of the 130 patients treated with cyclophosphamide, 42 (32%) were treated in tertiary-referral centres, and 88 (68%) were treated in non-tertiary centres. The correct dose of i.v. cyclophosphamide was given in 23/32 (72%) of patients treated in tertiary-referral centres, compared to 29/57 (51%) of patients treated in non-tertiary centres (p=0.05). Infections requiring hospital admission occurred in 9 (21%) of patients treated in tertiary-referral centres, compared to 24 (27%) of patients treated in non-tertiary centres (p=0.5). Patients who received Rituximab were more commonly treated in tertiary-referral centres (48 (63%)) compared to 28 (37%) treated in non-tertiary centres. PJP prophylaxis was prescribed to 73% of patients on Rituximab treated in tertiary-referral centres compared to 52% treated at non-tertiary centres (p=0.07).

Discussion

Main findings

We identified a cohort of 213 patients receiving routine clinical care for AAV in a large health region of England. We found long delaysbetween admission and diagnosis in some in-patients diagnosed with AAV (max >7 weeks). We found that a guideline recommended dose of i.v. cyclophosphamide, based on age, weight and renal function, was prescribed in <60% of patients, and that adherence to other safety standards for monitoring and prophylactic medication had room for improvement. Rituximab treatment was prescribed to eligible patients in compliance with the NICE technology appraisal and NHS England commissioning policy, but there was opportunity to improve the numbers of patients co-prescribed PJP prophylaxis as is recommended in the SPC. We found that delay between diagnosis and starting immunosuppressive treatment and prescription of the correct dose of cyclophosphamide were significantly better in tertiary-referral centres which provided care for much larger numbers of patients than non-tertiary centres.

We found that 25% of patients on cyclophosphamide were admitted with infection during or in the 6 months after cyclophosphamide treatment, which is higher than expected based on previous studies[6–8]. Our best estimates of the

effect of giving cyclophosphamide by the p.o. compared to the i.v. route, once adjusted for the effects of age and renal involvement, were that it increased infections by 80% and risk of death by 70% – but our confidence intervals were wide as our sample size is small and these were not statistically significant.

Strengths and limitations

This is the largest collaborative audit of a rare autoimmune rheumatic disease, and the first time services for people with AAV have been able to benchmark their care not just against standards, but also against other providers. Its main strength is in the large and unselected group of patients who were diagnosed with AAV by their rheumatologist or renal physician, across a range of different sized healthcare providers ranging from smaller district general hospitals to large tertiary-referral centres. It therefore enables a representative overview of the process and outcome of care in England, which cannot be adequately gained from existing clinical trial reports or cohorts from single centres.

As it is an audit there are limitations, particularly incomplete case capture. Cases were contributed by 20 (59%) of 34 invited units. A cohort of 130 newly diagnosed adult patients were identified over 21 months in an adult catchment population of 6,980,000, which equates to an incidence rate of 10.6 per million person years, suggesting we identified ~50% of all expected incident cases [9] which compares favourably with the first year of the national Rheumatoid and Inflammatory Arthritis audit which captured about 42% of expected cases[10]. The demographics of cases included in the audit were very similar to a recent epidemiological study [11], and were received from the expected mix of district general and tertiary-referral hospitals. Data were collected and entered by a large team of people, which may lead to variation in interpretation of the questions, however a set of explanatory notes covering each question minimised this risk (online supplement). There are some missing data, particularly for baseline demographics as these were collected later, however the main outcomes have no missing data due to the electronic form not allowing submission until all questions were answered.

The audit captured data from patients treated between April 2013 and December 2014, whilst the BSR, NHS England and NICE standards were introduced during this period, although CYC dosing guidance is identical to the 2007 guideline. This

might explain the low use of BVAS to document outcomes (which these documents recommend/require). BVAS training can be completed online[12], and BVAS takes less than 3 minutes to complete[13]. It is possible that care has improved post-audit as a response to these guidelines.

Real life audit comparisons to clinical trials.

Our audit is the first description of routine care of patients with AAV across a large health region, and compliance with safety standards. The baseline characteristics of included patients are similar to other UK epidemiological studies from the Midlands and Norfolk [11,14]. Our cohort also had similar remission[6] (83%) and survival rates (1 year survival 90.8%) to other studies [8,15–17].

Of note, our audit of routine practice found higher rates of serious infection than in the EUVAS clinical trials[18]. This is likely to be influenced by selected populations, and possibly by protocolised treatment in clinical trials. For example, the CYCLOPS trial reported 11% of patients had severe infections requiring hospital treatment during median 18 months follow-up, so the follow up time was longer than in our audit, and the trial excluded those with creatinine >500 μmol/L, and age<18 or >80 which are risk factors for serious infection[6]. Based on these exclusion criteria alone, 7% of the patients included in our audit would have been excluded from CYCLOPS. Our results are similar to a recent study of all patients presenting to a single centre, where 22% of patients receiving cyclophosphamide for AAV were admitted with infection during the first year after commencing treatment[19]. This suggests 22-25% may be a realistic estimate of the risk of hospitalisation with infection in the year after starting cyclophosphamide that patients should receive counselling about pre-treatment.

We did not find a statistically significant increased risk of infection and death in patients treated with p.o. compared to i.v. cyclophosphamide, however, our audit was under-powered for this analysis. A previous meta-analysis of 3 randomised controlled trials comparing p.o. vs i.v. cyclophosphamide found i.v. cyclophosphamide conferred a significantly lower risk of infection (OR 0.45, 95% CI 0.23-0.89) [20]

Our findings reflect some of the findings common to rare diseases, which are highlighted in the UK Strategy for Rare Diseases[21]. For example, people with

rare diseases are often slow to benefit from advances in treatment[21], and it is notable that although the minority of patients (41%) overall were treated at tertiary-referral centres, the majority of patients receiving Rituximab (63%) were treated in tertiary referral centres. Although, tertiary referral centres are more likely to treat severe disease, they may also be quicker to embrace new treatments, facilitated by these centres fulfilling the 'specialised centre' requirements of the NHS England policy for access to this drug.

Clinical implications and Conclusion

We identified opportunities to improve our care, including improving compliance with safety standards for the delivery of cyclophosphamide for the 42% of patients who received an incorrect dose of i.v. cyclophosphamide. Our comparison of p.o. versus i.v. cyclophosphamide adds to the level of certainty from other studies that p.o. cyclophosphamide has higher toxicity. Development of a national treatment protocol / checklist to reduce heterogeneity in care should be considered as a priority. More than half of patients were diagnosed as inpatients, and we found a long delay between admission and diagnosis in some patients (up to 53 days). Increased awareness among acute admitting physicians, and earlier ANCA-testing could reduce diagnostic delay and perhaps reduce organ damage among newly diagnosed patients. Our finding that 25% of patients on cyclophosphamide were admitted with infection during or following cyclophosphamide therapy is higher than in clinical trials, and requires increased vigilance for infection, and changes to the expectations we give patients when counselling them before starting treatment.

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Conflicts of interest

No authors declared conflicts of interest, financial or otherwise, with respect to this work.

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Table 1: Newly diagnosed patients (n=130)

Characteristic	
Age, median (IQR), years	67 (56-73)
Female	52 (43)
Male	68 (57)
GPA	57 (49)
MPA	49 (42)
EGPA	10 (9)
PR3-ANCA	52 (43)
MPO-ANCA	55 (45)
ANCA negative	9 (8)
p-ANCA only (not PR3/MPO)	3 (3)
c-ANCA only (not PR3/MPO)	1 (1)
BVAS organ system	**Involved at diagnosis**
Constitutional symptoms	88 (73)
Renal	76 (63)
Chest	62 (50)
ENT	55 (47)
Cutaneous	30 (25)
Nervous system	28 (23)
Mucous membranes / Eyes	20 (17)
Abdominal	13 (11)
Cardiovascular	8 (7)
Audit outcomes	
Delay from 1st symptom to diagnosis, median (IQR), months	2.6 (1.2-6.1)
BVAS score recorded	
At diagnosis	10 (8)
At 6 months	8 (7)
First choice of remission induction treatment	
Cyclophosphamide	99 (76)
Rituximab	6 (5)
Other agent	25 (19)
Glucocorticoids	
Prednisolone at diagnosis, median (IQR), mg	55 (40-60)
Additional i.v. methylprednisolone	60 (46%)
Prednisolone at 6 months, median (IQR),mg	10 (5-10)
Remission at 6 months	101 (83)
Survival at 1 year	
All patients (n=130)	90.8% (95% CI 84.3-94.7)
Patients with documented renal involvement (n=76)	85.5% (95% CI 75.4-91.7).

Values are n (%) unless otherwise stated.

GPA granulomatosis with polyangiitis, MPA microscopic polyangiitis, EGPA eosinophilic granulomatosis with polyangiitis

Table 2: Risk of infection and death in newly diagnosed patients treated with p.o. compared to i.v. cyclophosphamide

	Infection			Mortality		
CYC route	N (%)	Crude OR for infection	Adjusted OR[a]	N (%)	Crude HR for death	Adjusted HR[a]
i.v.	15/74 (20.2)	1	1	9/74 (12.2)	1	1
p.o.	9/25 (36.0)	2.2 (0.8-6.0)	1.8 (0.6-5.1)	6/25 (24.0)	2.3 (0.8-6.5)	1.7 (0.5-5.3)

[a]Adjusted for age and renal involvement. CYC cyclophosphamide, OR odds ratio from logistic regression, HR hazard ratio from Cox regression.

Table 3: Patients treated with Cyclophosphamide for new diagnosis or relapse (n=130)

Characteristic	
Age, median (IQR), years	65 (56-72)
Female	50 (42)
Male	68 (58)
GPA	64 (58)
MPA	39 (35)
EGPA	8 (7)
PR3-ANCA	58 (49)
MPO-ANCA	46 (39)
ANCA negative	8 (7)
p-ANCA only (not PR3/MPO)	4 (3)
c-ANCA only (not PR3/MPO)	2 (2)
Treatment	
p.o. cyclophosphamide	29 (22)
i.v. cyclophosphamide	101 (78)
Audit outcome	
Correct dose of i.v. cyclophosphamide, within 100mg	50 (58)
Underdosed, >100mg	32 (34)
Overdosed, >100mg	13 (8)
FBC was checked 7-10 days after the first dose	119 (92)
Total cumulative dose of cyclophosphamide, median (IQR), g range	6 (4-9) 0.1-21g
Co-prescription of Mesna	99 (76)
Co-prescription of PJP prophylaxis	106 (82)
Admission with infection during or within 6 months of cyclophosphamide therapy	33 (25)

All values are n (%) unless otherwise stated.
GPA granulomatosis with polyangiitis, MPA microscopic polyangiitis, EGPA eosinophilic granulomatosis with polyangiitis, FBC full blood count, PJP pneumocystis jiroveci pneumonia

Table 4: Patients treated with Rituximab for new diagnosis or relapse (n=76)

Characteristic	
Age, median (IQR), years	50 (36-63)
Female	34 (47)
Male	39 (53)
GPA	60 (82)
MPA	11 (15)
EGPA	2 (3)
PR3-ANCA	60 (82)
MPO-ANCA	11 (15)
ANCA negative	1 (1)
p-ANCA only (not PR3/MPO)	1 (1)
c-ANCA only (not PR3/MPO)	0
Treatment	
Rituximab given for New diagnosis[a]	16 (21)
Regimen	
1 g x2	15 (94)
375mg/m2 x4	1 (6)
Diagnosis, %	
GPA	67
MPA	33
EGPA	0
Rituximab given for relapse	60 (79)
Regimen	
1g x2	35 (58)
375mg/m2 x4	16 (27)
1g x1	7 (12)
Diagnosis	
GPA	95
MPA	2
EGPA	2
Audit outcomes	
Treated at referral centres	48 (63)
Treated at other centres	28 (37)
Immunoglobulins checked prior to treatment	63/68 (93)
Co-prescription of PJP prophylaxis	49 (65)
Met NICE TA / NHS England eligibility criteria	74 (96)

All values are n (%) unless otherwise stated. [a]First choice treatment (n=6), after switching (n=10). GPA granulomatosis with polyangiitis, MPA microscopic polyangiitis, EGPA eosinophilic granulomatosis with polyangiitis, PJP pneumocystis jiroveci pneumonia, NICE National Institute for Health and Care Excellence, TA technology appraisal, NHS National Health Service

Table 5: Comparison of Referral and non-referral centres

	Referral Centres	Non-referral Centres	p-value
Newly diagnosed patients, n (%)	45 (35)	84 (65)	
Delay between admission & diagnosis, median (IQR)	4 (2-13)	7 (4-11)	0.4
Delay between diagnosis and starting immunosuppression, median (IQR)	4 (3-10)	9 (3-19)	0.01
Patients treated with Cyclophosphamide, n (%)	42 (32)	88 (68)	
Correct dose of i.v. cyclophosphamide	23/32 (72)	29/57 (51)	0.05
Admission with infection during or within 6 months of cyclophosphamide therapy, n (%)	9 (21)	24 (27)	0.5
Patients treated with Rituximab, n (%)	48 (63)	28 (37)	
Co-prescription of PJP prophylaxis, %	73	52	0.07

PJP pneumocystis jiroveci pneumonia