Treatment outcomes of ANCA-associated vasculitis in patients over age 75 years: a meta-analysis

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Short title: Treatment outcomes of AAV in patients $\geq$ 75 years

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Background: The benefits of treating ANCA-associated vasculitis (AAV) in advancing age remains unclear with most published studies defining elderly as ≥65 years. This study aims to determine outcomes of induction immunosuppression in patients aged ≥75 years.

Method: A cohort of patients aged ≥75 years with a diagnosis of AAV between 2006-2018 was constructed from two centres. Follow up was to two years or death. Analysis included multivariable Cox regression to compare mortality and ESRD based on receipt of induction immunosuppression therapy with either cyclophosphamide or rituximab. A systematic review of outcome studies was subsequently undertaken amongst this patient group through Pubmed, Cochrane and Embase databases from inception until 16/10/19.

Results: 67 patients were identified. Mean age was 79 ± 2.9 years and 82% (n=55) received induction immunosuppression. Following systematic review, four studies were eligible for inclusion, yielding a combined total of 290 patients inclusive of our cohort. The aggregated one year mortality irrespective of treatment was 31% (CI 25% - 36%). Within our cohort, induction immunosuppression therapy was associated with a significantly lower two-year mortality risk [HR 0.29 (95% CI 0.09 – 0.93)]. The pooled HR by meta-analysis confirmed this with a significant risk reduction for death [HR 0.31 (95% CI 0.16 - 0.57), I^2=0%]. Treated patients had a lower pooled rate of ESRD, but was not statistically significant [HR 0.71 (95% CI 0.15 – 3.35)].

Conclusion: This meta-analysis suggests that patients ≥75 years with AAV do benefit from induction immunosuppression with a significant survival benefit. Age alone should not be a limiting factor when considering treatment.

Introduction

ANCA-associated vasculitis (AAV) tends to present with rapidly progressive renal disease, carrying a significant risk of morbidity and mortality with a poorer survival probability in those patients requiring renal replacement therapy at presentation (1). Current established immunosuppressive therapies are effective with improved patient and renal survival (2, 3), but their use requires careful patient selection when balanced against the potential risks, with up to 60% of deaths in the first year resulting from adverse effects of treatment (3, 4).

Advancing age is often considered to be a negative predictor for death and end stage renal disease (ESRD) when considering treatment in patients with AAV (5, 6). This is based on the outcomes of previously published observational studies and randomised control trials, most of which tended to categorise older age as greater than 65 years and may not provide an accurate representation of those with advancing age (4, 6-8). Subsequently, despite being a disease that predominantly effects the elderly, as well as the most common cause of biopsy proven acute kidney injury in patients over the age of 80 years, the benefit of treating AAV in older age groups remains unclear (9-12). This study attempts to address this by evaluating treatment outcomes in patients ≥75 years with AAV from two centres with subsequent systematic review and meta-analysis of the published literature.

Materials & Method

Participants & Study design

A cohort of consecutive patients aged ≥75 years with a diagnosis of AAV between 2006-2018 was constructed from two centres; one in the United Kingdom (UK) and one in the United States of America. All participants had renal impairment secondary to AAV at the time of diagnosis. Those with missing data or dual positivity for both ANCA and anti-GBM antibodies were excluded. For the remaining patients, the following data was retrospectively collected from the time of diagnosis; demographics, clinical presentation, modified Charlson comorbidity index (CCI) (13, 14), histopathology, immunosuppression therapy, patient outcomes and laboratory values including ANCA specificity, serum creatinine and estimated glomerular filtration rate (eGFR). As renal and connective tissue disease were the conditions of interest in our cohort, a modified CCI that did not include these in its calculation was used. Total score could range from 0 to 32. eGFR was calculated using the Modified Diet in Renal Disease equation (15). Cause of death was attained from review of medical records and categorised as follows; infection, active vasculitis, cardiovascular disease, respiratory disease, peripheral vascular disease, cerebrovascular disease, malignancy and unknown cause.

Patients were categorised into two groups; those who received induction therapy and those who did not. Induction therapy was defined as regimes utilising either cyclophosphamide or rituximab. The dosing regimen of intravenous cyclophosphamide adopted in both centres adjusted for renal function and patient age in accordance with recommendations made by the European vasculitis study group (16, 17). Depending on local practice, rituximab was administered at a dose of 375mg per square meter of body surface area per week for four weeks or as 1g every two weeks for two doses. Pulsed intravenous methylprednisolone and plasma exchange were administered according to local physician discretion. The cumulative dose range of methylprednisolone was 0.5-3g. Considerations for plasma exchange included dialysis dependence, serum creatinine >500 µmol/L or pulmonary haemorrhage. This retrospective cohort study received ethical approval from the UK Health Research Authority and Confidentiality Advisory Group and institutional review board at Johns Hopkins Hospital.

Outcomes

The primary outcomes were risk of ESRD, death and the composite outcome of death or ESRD within two years of follow up. ESRD was defined by continued use of renal replacement therapy at follow up. Secondary outcomes included serious adverse events and renal recovery. Serious adverse events of therapy were defined as infection requiring hospitalisation, new onset malignancy, thrombocytopenia, leukopenia, bone marrow suppression and complications of glucocorticoid therapy including new onset diabetes mellitus, osteoporosis and osteoporotic fractures. Renal recovery was defined as sufficient improvement in renal function to achieve dialysis independence. Renal histopathology was categorised according to the Berden histopathological classification system (18).

Systematic review & study selection for meta-analysis

A systematic review was undertaken to identify any studies evaluating outcomes in patients aged ≥75 years with AAV. Pubmed, Cochrane and Embase databases were each searched independently by two reviewers (AM & ME) from inception until 16.10.2019 using the following search strategy; *"ANCA"* OR *"anti-neutrophil cytoplasmic antibody"* OR *"vasculitis"* OR *"PR3"* OR *"MPO"* OR *"ANCA-associated"* AND *"elderly"* OR *"old"* OR *"75 years"* OR *"geriatric"* AND *"ESRD"* OR *"end stage renal disease"* OR *"dialysis"* OR *"death"* OR *"survival"* OR *"mortality"* OR *"renal replacement therapy"* OR *"outcome"*. All outcome studies on patients ≥75 years with AAV, inclusive of those presenting data as a subgroup analysis, were included. Case reports, editorials, letters to the editor, review articles, conference abstracts and studies not published in English were excluded from review. Eligible studies were independently screened and reviewed by two authors. In instances of disagreement, resolution by consensus was sought. The methodological quality and risk of bias of eligible studies was assessed using the Newcastle-Ottawa scale for observational studies. The protocol for this review was registered and published on PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019123279).

Two investigators independently undertook data extraction using a predefined criterion. The study characteristics extracted for inclusion in meta-analysis were as follows; year of publication, study type, sample size of participants aged ≥75 years, male percentage, the number of participants who received induction immunosuppression, follow up period, the rate of death and ESRD at one and two years, the rate of serious adverse events and the hazard ratios for death and ESRD in treated and untreated participants.

Statistical analysis

Patient characteristics were presented as mean ± SD or median for continuous variables and proportions for categorical variables. A comparison between treated and untreated groups were analysed utilising t-Tests, Mann-Whitney, chi- squared or Fisher exact tests where appropriate. Patient survival times were calculated from the point of diagnosis until death, two years, loss to follow up or end of study (01/12/2018). Renal survival was calculated similarly with the addition of censor for death. The risk of death, ESRD and death or ESRD were studied using univariate and multivariable cox regression models, presented as hazard ratios (HR) with 95% confidence intervals (CI). The following parameters were adjusted for in the final model; use of induction immunosuppression, gender, CCI, eGFR at the time of diagnosis and the presence of renal limited disease. Gender and co-morbidity index were selected to reflect patient characteristics. eGFR was selected an indicator of disease severity and predictor of renal outcome. Renal limited disease was selected as a predictor variable as the absence of multi-system disease may confer a survival advantage. Univariate Kaplan-Meier curves were constructed to complement the cox regression hazard models for death, ESRD and death or ESRD. The rate of serious adverse events and impact of intravenous methylprednisolone were analysed utilising t-tests, Mann-Whitney, chi-squared or Fisher exact tests where appropriate.

The systematic review was conducted in accordance with PRISMA guidelines. A random effects meta-analysis model was used to calculate pooled HR for ESRD and death by treatment status. Study heterogeneity was evaluated using chi- square with a significance level of $P<0.10$ and I^2 statistics. Thresholds for I^2 statistics were as follows; low (25-49%), moderate (50-74%) and high (>75%).

Results

Study Population

Follow up data was completed in 67 patients aged ≥75 years, of which 98.5% (n=66) had disease confirmed on renal biopsy. Descriptive baseline characteristics for this cohort according to treatment status are shown in Table 1. Mean age was 79 ± 2.9 years with a mean follow up period of 1.7 ± 0.62 years. Renal biopsy data was available in 94% of patients (n=63) with focal disease as the most common histological subtype as defined by the Berden classification (18). Just under half of patients had renal limited disease and ANCA serology was positive in 86.6% of patients (n=58) with a predominance for MPO serotype.

Induction immunosuppression with cyclophosphamide or Rituximab was given to the majority of patients (82%). All received concomitant oral steroids and cyclophosphamide was the most commonly used agent with a median cumulative dose of 2.73g (interquartile range 7.14–1). 3 patients failed treatment with cyclophosphamide and warranted continued therapy with rituximab. The non-induction cohort consisted solely of patients from the UK centre. Amongst this group, three patients received alternative oral immunosuppression at the time of diagnosis; two with azathioprine and steroids, one with steroids alone. From the induction and non-induction cohorts, 44 and 9 patients were alive and dialysis independent at 6 months, respectively. Maintenance therapy amongst these patients is shown in Table 1.

A total of thirty-three patients received intravenous methylprednisolone; 56.4% (n=31) vs. 16.7% (n=2) in the induction and non-induction therapy cohorts respectively. Dosing data was available in twenty-nine patients with mean dose of 2.24 $\pm$ 0.8 grams across both groups. Twelve (21.8%) patients in the induction therapy cohort received plasma exchange with treatment data available in ten cases. The median number of sessions administered was five. No patients in the non-induction therapy cohort received plasma exchange. Of the 67 patients in our cohort, 26 were aged $\geq$80 years with 88.5% (n=23) receiving induction immunosuppression.

Outcomes of study population

Clinical outcomes according to treatment status are outlined in Table 2. Three patients (4.5%) died within the first three months of diagnosis, of which only one received induction therapy. The overall one and two-year survival rates irrespective of treatment were 79.1% (n=53) and 76.1% (n=51) respectively. The use of induction immunosuppression was associated with a significant reduction in the risk of death [HR 0.29 (95% CI 0.09–0.93)] (Table 3). Of the 16 deaths at the end of the two-year follow up period, one confirmed case was attributable to underlying vasculitic disease. The leading cause of death in the non-induction cohort cannot be commented on due to incomplete data with an unknown cause of death in 80% (n=4) of cases. Amongst those receiving induction therapy, infection was the leading cause of death.

Eighteen patients (26.9%) required dialysis within thirty days of their initial presentation, with no new cases of dialysis dependence beyond this point throughout the follow up period. Of these patients, 15 received induction immunosuppression, with four recovering renal function by twelve months. At the end of the two year follow up period the rate of ESRD was 20% (n=11) and 16.7% (n=2) in the induction and non-induction cohorts respectively. In multivariable cox regression analysis, renal survival was similar between the two groups [HR 1.17 (95% CI 0.25–5.54)] (Table 3). A higher eGFR at the time of initial diagnosis was associated better renal survival [HR 0.75 (95% CI 0.63–0.89)] (Table 3).

The therapeutic benefit of induction immunosuppression was maintained on assessing the composite outcome of death or ESRD ([HR 0.33 (95% CI 0.12–0.86)] (Table 3). Supplementary figures 1-3 depicts univariate Kaplan-Meier survival curves for death, ESRD and death or ESRD by induction immunosuppression.

On subgroup evaluation of patients $\geq$80 years, 88% (n=23) received induction immunosuppression with a mortality rate of 21.7% (n=5) and all deaths occurring within 12 months of diagnosis. Acknowledging that analysis may be limited the small sample size, use of induction immunosuppression did not confer a higher risk of death in this group upon restricting the multivariable cox regression model to those aged >80 years [HR 0.01 (95% CI 0–0.84)] (supplementary Table1). No deaths or episodes of ESRD occurred within the first year in untreated patients $\geq$80 years.

No instances of death or ESRD occurred in those patients receiving rituximab. Meaningful analysis of cyclophosphamide versus rituximab as outcome predictors was limited. Twenty-eight patients (41.8%) experienced serious adverse events, comprising of 22 patients from the induction cohort and 6 from the non-induction cohort. Overall, infection accounted for the majority of cases. The use of induction immunosuppression did not confer a higher risk of serious adverse events (p=0.54). Similarly, the rate of adverse events did not significantly differ between those patients who received intravenous methylprednisolone and those who did not; 42.9% (n=12) vs. 57.1% (n=16) respectively (p=0.46).

Systematic Review & Study Selection

The process of study selection is outlined in supplementary Figure 4. Thirteen citations qualified for full text review. Nine were published as abstracts only and subsequently excluded. Characteristics of the four remaining eligible studies are summarised in supplementary Table 2.

Only three studies categorised patients according to the use of immunosuppressive therapy; Bomback *et al*, Weiner *et al* and Sato *et al,* with an aggregated total of 175 patients receiving induction immunosuppression (19-21). The most commonly used agent was cyclophosphamide (72.6%) with the majority receiving oral therapy (59%). Statistical analysis with stratification according to the use of induction immunosuppression was undertaken by two studies; Weiner *et al* and Bomback *et al* (19, 20). The control group in Weiner *et al* consisted of untreated patients as well as those receiving alternative regimes such as azathioprine, methotrexate or mycophenolate. The control group in Bomback *et al* consisted of untreated patients only.

Meta-analysis results

With the addition of our cohort, a sample size of 290 patients aged ≥75 years with AAV were available for review. The one year mortality rate irrespective of treatment was 31% (CI 25%-36%). Weiner *et al* and Bomback *et al* both used multivariable cox models to analyse the hazard of death and ESRD with induction therapy. Their results in conjunction with the findings from our presented cohort were used to present the pooled HR for death and ESRD by meta-analysis in 258 patients. The use of induction immunosuppression demonstrated a significant benefit for patient survival with a pooled hazard ratio for death of 0.31 (95% CI 0.16-0.57) [I^2 = 0 %] (Figure 1). Induction therapy was also associated with a lower pooled rate of ESRD, although not statistically significant [HR 0.71 (95% CI 0.15–3.35)] (supplementary Figure 5). Serious adverse events were available for two studies with a combined cohort of 105 treated patients and an incident rate of 38.1% (n = 40).

Discussion

To date there has been limited published data guiding treatment outcomes of AAV in older populations and the potential benefit of utilising established induction immunosuppression in those aged ≥75 remains poorly defined.

This represents an area of increasing clinical need owing to an overall rise in the both the incident and prevalence of disease, with the former rising from 8-10/million to 13-20/million over recent years (9, 10, 22). The present study addresses this by reporting the experiences of two centres followed by a meta-analysis of published studies. In doing so we identified a clear survival benefit in patients $\geq$ 75 years treated with induction immunosuppression with either Cyclophosphamide or Rituximab.

Within the first twelve months of treatment, the greatest risk to patient survival is adverse effects of therapy rather than active vasculitis, with up to 60% of deaths resulting from infection (4, 8). It is considered that with increasing age, a patient's ability to tolerate any significant immunosuppression is reduced with a higher propensity to succumb to such adverse effects. Although not by study design, recent landmark trials in the management of AAV have tended to only include patients under the age of 75 years (17, 23-25) and to date the majority of observational studies reviewing the outcome of patients with AAV have often considered older age as being greater than 65 years (2, 5-7, 26, 27). These have identified age $\geq$65 years as a poor prognostic marker for patient outcomes and in view of this, it would be anticipated that patients older than 75 years would fare even worse.

In a retrospective single centre study evaluating one-year outcomes in patients over the age of 80 years, Bomback *et al* demonstrated that treatment can prolong dialysis free survival with a remission rate of 49% and up to 37% fewer patients reaching ESRD at one year compared to the untreated cohort (19). Although the cumulative mortality rate was 49%, with most patients dying from infection rather than underlying disease, the risk of death at one year was 17% lower in treated patients (19). While this difference was not statistically significant, follow up beyond one year identified a significantly lower risk for both ESRD and death. In a similar study, Weiner *et al* evaluated the two-year survival in patients over the age of 75 years in a multi-centre retrospective study (20). Their survival analysis supported that of Bomback *et al*, identifying superior patient survival in those given induction therapy with 36% fewer deaths and a significantly lower hazard ratio for death on multivariable analysis (20). This remained unchanged on subgroup analysis of patients who received a lower cumulative dose of cyclophosphamide.

Within our cohort analysis, we exhibited comparable findings to previous studies with a significantly lower hazard ratio for death in treated patients. The survival benefit of induction immunosuppression persisted despite advancing age following subgroup analysis of those aged $\geq$80 years. There was no demonstrable benefit for renal survival. The burden of co-morbidity was similar between the two groups and parallel to the findings of Bomback *et al,* renal function at the time of diagnosis was predictive of outcomes. When considered in light of the findings of Bomback *et al,* the current evidence suggests that on its own advancing age $\geq$80 years should not discount patients from treatment and that despite a higher potential risk of adverse effects, certain selected elderly patients may benefit from induction immunosuppression in AAV.

The present meta-analysis of these observational studies confirmed a clear survival advantage of induction immunosuppression over no/other oral immunosuppression in patients $\geq$75 years with AAV. Similarly, a lower rate of ESRD with treatment was shown, although this did not reach statistical significance. In view of these findings, the safe use a reduced dose of cyclophosphamide applied in both our cohort and Wiener *et al* suggests that the dosing regimen described by previous studies can safely be adopted in older patients, with sufficient mitigation of risk without compromising therapeutic benefit (4, 6, 7).

The remaining two studies of Hoganson *et al* and Sato *et* al identified on systematic review were not included in meta-analysis (21, 28). Sato *et al* was a comparative study evaluating treatment outcomes of AAV in patients aged $\geq$75 years against those < 75 years. In the cohort described, patients $\geq$75 years numbered ten, of which 80% did not receive induction therapy with either Cyclophosphamide or Rituximab (21). This was despite presenting with more severe vasculitic disease due to the presumption that they were more susceptible to adverse events. The implication of this selection bias is acknowledged by the authors when concluding a poorer survival rate in elderly patients. The limitation of this study design could have affected our presented pooled one year survival rate, however it did not have any implication on our subsequent meta-analysis with no stratification of outcomes by treatment status. Similarly, data from Hoganson *et al* was excluded from meta-analysis on the same basis.

Despite improved patient survival with induction immunosuppression, the question remains, at what cost is this achieved. Amongst other factors, advancing age has previously been associated with a higher degree of long term damage and this patient group are potentially more frail with increased susceptibility to any potential treatment related morbidity (29). In a follow-up study of their previously reported cohort, Weiner *et al* set out to address this by evaluating the potential association between end organ damage and hospitalisation rates with therapy at one and two years (30). In doing so, they identified that amongst patients $\geq$75 years the use of cyclophosphamide or rituximab was actually associated with a lower rate of damage (30). As disease severity at presentation is known risk factor for permanent organ damage (29), this finding likely reflects the benefit of attenuated disease activity achieved with therapy. There was no increased rate of hospitalisation or length of stay within 12 months of treatment (30).

The potential for treatment related damage secondary to glucocorticoids is widely accepted and reported (29, 31). Although our study showed no increased risk of adverse event secondary to methylprednisolone exposure, this is likely limited by our relatively small sample size. In their more recent study, Weiner *et al* did identify an association between treatment related damage and fatal infections with a higher cumulative steroid exposure within the first three months of therapy. Taking this into account in conjunction with the findings of our study, it may be that future treatment strategies of AAV in advancing age would benefit more from minimising steroid exposure, as opposed to avoidance or further modification of current therapy with rituximab or reduced dose cyclophosphamide.

The findings of our study should be considered in context of its limitations. Firstly, the lack of randomised control trials and the retrospective design of all included studies limits the level of evidence that could be derived from them. Secondly, we acknowledge that the modified CCI scores observed in our cohort were seemingly low. In a previous small study applying a similar modified CCI to ours at diagnosis, with the exception of weighted score for age, a higher score was associated with reduced patient and renal survival. In this study, patient age ranged from 18-76 years with a mean age of 53.2 $\pm$ 15.63 years and mean CCI at diagnosis of 4.9 $\pm$ 2.49 (14). The lower mean CCI scores observed in our cohort would indicate a less comorbid and potentially less frail population, which would favour better outcomes and should be taken into account when interpreting our cohort results. Thirdly, allocation of treatment varied in each centre based on local expertise and clinical assessment which may have imposed a significant selection bias: a factor evident by the imbalance of untreated patients between our two centres which restricted adjustment for centre effect in the final models. This likely reflects individualisation of care based on recognition of frailty and suitability of immunosuppressive therapy; an aspect of clinical assessment which is not captured by measures such as the modified Charlson comorbidity index. A potential tool that could account for this is the Clinical Frailty Scale, a frailty screening method that has recently been validated in patients with chronic kidney disease. Its incorporation in future prospective studies could help stratify this crucial aspect of clinical judgement, further guiding future immunosuppressive therapy in renal vasculitis (32). Fourthly, statistical analysis to adjust treatment outcome according to the histological pattern of disease could not be undertaken due to limited variability and small sample size. This is a factor which may have influenced treatment decisions. These limitations should be weighed the rigorous and systematic approach of this study, as well as the previously limited data guiding treatment in our defined population.

The question of whether or not induction immunosuppression is of more harm than benefit in patients with AAV and advancing age is of increasing importance. The data presented here from our centres and pooled results from meta-analysis suggests that patients $\geq$75 years with AAV do benefit from induction immunosuppression, with a significant survival advantage within the first two years of therapy. Age alone should not be a limiting factor when considering treatment. Future trials in AAV may benefit from increasing the upper age limit at which patients are considered elderly to 75 years in order to attain more representative data.

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Ethics: This retrospective cohort study received ethical approval from the UK Health Research Authority and Confidentiality Advisory Group and institutional review board at Johns Hopkins Hospital. The study was conducted in accordance with the declaration of Helsinki.

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Figure Legends:

Figure 1 – Forest plot of mortality risk in patients with ANCA-associated vasculitis aged ≥ 75 years based on the use of induction immunosuppression

Supplementary Figure 1 – Kaplan-Meier survival curves for the outcome of death according to the use of induction immunosuppression therapy. Curves reflect univariate analysis

Supplementary Figure 2 – Kaplan-Meier survival curves for the outcome of end stage renal disease (ESRD) according to the use of induction immunosuppression therapy. Curves reflect univariate analysis

Supplementary Figure 3 – Kaplan-Meier survival curves for the composite outcome of death or end stage renal disease (ESRD) according to the use of induction immunosuppression therapy. Curves reflect univariate analysis

Supplementary Figure 4 – Flow diagram of systematic review and study selection for meta-analysis

Supplementary Figure 5 – Forest plot of ESRD risk in patients with ANCA-associated vasculitis ≥ 75 years based on the use of induction immunosuppression