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Full Review

Getting the balance right: adverse events of therapy in anti-neutrophil cytoplasm antibody vasculitis

Limy Wong[1], Lorraine Harper[2] and Mark A. Little[1]

[1]Trinity Health Kidney Centre, Tallaght Hospital and Trinity College, Dublin, Ireland and [2]Division of Medical Sciences, University of Birmingham, Birmingham, UK

Correspondence and offprint requests to: Limy Wong; E-mail: limywong@gmail.com; limywong@beaumont.ie

ABSTRACT

Antineutrophil cytoplasm antibody associated systemic vasculitides (AASV) have traditionally been managed with a combination of cyclophosphamide and glucocorticoids during the induction phase, followed by azathioprine in the maintenance phase. Whilst these therapies have markedly improved the prognosis in AASV, treatment related adverse events remain a major challenge and include complications such as infection, glucocorticoid related side effects, malignancy, cardiovascular disease, infertility and death. Newer biologic therapies have been shown to demonstrate equivalent efficacy as cyclophosphamide for remission but the hoped for reduction in adverse events has yet to be realised. More recent efforts have been focused on refining existing therapeutic regimens and strategies, tailoring individual treatment to disease severity, patient age and kidney function to derive maximum treatment efficacy while minimising treatment toxicity. In particular, current interventional trials are targeting a reduction in corticosteroid exposure in an effort to make induction and maintenance regimens safer.

Keywords: adverse events, treatment, vasculitis

INTRODUCTION

Anti-neutrophil cytoplasm antibody (ANCA)-associated systemic vasculitis (AASV) most commonly occurs in the elderly, with a peak age of onset between 65 and 74 years [1]. In Europe, the annual incidence is 11–16 cases/million with a prevalence of 177 cases/million [2]. It commonly affects the respiratory tract and kidneys and is the most common cause of rapidly progressive glomerulonephritis [1]. Therefore, many affected individuals have varying degrees of excretory renal insufficiency which, combined with advanced age and use of toxic therapeutic agents, creates a potent environment of altered pharmacokinetics and pharmacodynamics, and an elevated risk of adverse events of therapy.

HISTORICAL PERSPECTIVE ON TREATMENT DEVELOPMENT

The goals of therapy are to achieve remission from active vasculitis, preserve renal function, prevent relapse and minimize drug toxicity. The original NIH regimen of cyclophosphamide (CYC) 2 mg/kg/day and glucocorticoids (GC) 1 mg/kg/day resulted in a complete remission rate of 93% in 85 patients [3]. The relapse rate remained high, up to 50% over 5 years [4]. However, this induction regimen resulted in a high cumulative dose of CYC with a high degree of treatment-related toxicity and morbidity, especially when therapy was prolonged.

The last 20 years has seen attempts to reduce therapy toxicity by lowering exposure to CYC and GC, by the use of alternate immunosuppressives, and by adjusting the intensity of therapy to the severity of clinical presentation [5]. More recently, rituximab, a B-cell depleting monoclonal antibody, has entered widespread use. Treatment is organized into an induction phase to rapidly suppress disease activity and achieve a 'remission' in order to avoid further vital organ damage, rescue renal function and reduce constitutional disturbance [6]. This accepts a higher level of drug toxicity and often uses CYC or rituximab. In those with milder presentations alternative agents such as methotrexate or mycophenolate mofetil have utility. This induction phase lasts 3–6 months and is

followed by a longer remission maintenance phase when less toxic therapy is used, such as azathioprine or methotrexate. Prolonged follow-up is then required to manage the consequences of vasculitic damage, drug toxicity and increased cardiovascular and malignancy risk [7].

IMPACT OF ADVERSE EVENTS ON MORTALITY

The greatest risk to patients with AASV is in the first year following diagnosis and is currently from the adverse events of treatment, particularly infection, rather than from active vasculitis [8, 9]. An analysis of patients enrolled into four EUVAS studies showed a total of 56 deaths within the first 12 months, of which 28 were due to infection (mainly respiratory and blood stream), accounting for 50% of total events [9]. This has highlighted the importance of disease severity and accumulation of early adverse events, and has led to the development of a novel scoring system 'combined burden of events' (CBOE). This comprises three components: infection, leukopenia and other treatment-related adverse events. This triad, both together and individually, is a strong independent predictor of early mortality. Advanced age and the degree of renal impairment are strong independent predictors of adverse events, with risk rising exponentially with an estimated glomerular filtration rate (eGFR) <20 mL/min. Even after 1 year, infection was an important cause of death, causing 20% of reported deaths in this cohort. Cardiovascular disease (CVD) and malignancy also became common causes of death; active vasculitis was a rare cause of death in these patients [8].

Damage accumulation is an important predictor of long-term mortality. The vasculitis damage index (VDI), a validated checklist of 64 items in 11 organ-based systems, may be used to assess damage caused by the disease or treatment. Patients with ≥5 recorded items of damage have a 6.4-fold increase in risk of mortality [10]. Recording cumulative damage is important in predicting future risk for these patients. There is a complex relationship between the severity of vasculitis and the risk of developing adverse events, with eGFR being consistently found to be the greatest overall predictor. This is probably due to reduced excretion of active drug metabolites, as well as the general immunosuppressive effect of kidney failure. Therefore the 'one size fits all' therapeutic approach is not ideal and in the modern era of medical practice, a more personalized treatment approach, individualized to maximize treatment efficacy whilst minimizing adverse events, is desirable.

GLUCOCORTICOIDS: THE ELEPHANT IN THE ROOM?

GCs have traditionally been a major component of AASV induction and maintenance treatment. However, the optimal duration of GC use remains debated, with little evidence to guide this, and there is considerable variation in clinical practice patterns, particularly after remission induction. Importantly, GC therapy is associated with considerable adverse events. Within one year of diagnosis in those participating in the EUVAS trials, 8% suffered new onset diabetes (event rate 9.4/100 patient-years). Fractures (2.5%), avascular necrosis (0.4%), peptic ulceration (2.6%) and cataracts (2%) were also reported [9]. Damage, as quantified using the VDI tool, accrues with time and steroid side-effects are an important component of this damage: at long-term follow up (median 5 years) of 270 patients with data from this cohort, 41% had hypertension, 38% osteoporosis, 28% diabetes mellitus and 25% had developed cataracts [11]. It is difficult to differentiate the impact of GC therapy from other immunosuppressive agents on infection risk. In a French AASV cohort, 89% of serious infections occurred during GC treatment (variable doses), although there was also a relationship with CYC dosing in this study [12]. Further, prolonged exposure to GC (longer than 6 months) has been associated with a significantly increased risk of infection [13].

Although the goal must be early discontinuation of GC, this is not without risk and is relatively uncommon. Long-term data from EUVAS trials demonstrated that approximately half of the patients were on glucocorticoids beyond 2 years, with a mean duration of glucocorticoid use of 40.4 months [11]. A systematic review by Walsh *et al.*, which included 983 patients, detected a higher incidence of relapse in those where GC discontinuation was attempted within 12 months when compared to continued GC therapy (43 versus 14%, with 95% CI 33–52% and 10–19% respectively) [14]. However, this review had several limitations, particularly the presence of numerous confounding variables included in the meta-regression analysis, lack of a uniform definition of relapse amongst the analysed studies and the duration of GC dosing was not a primary variable in the included studies. Conversely, the study by McGregor *et al.*, [13] which compared those who had their GC withdrawn by 6 months with those who had not showed no increase in relapse with early GC withdrawal. However this was a small study of 120 patients and was not randomized.

It is now clear that patients with AASV have a high risk of CVD; 14% have a cardiovascular event within 5 years of diagnosis of AASV [15] and patients with AASV are more than twice as likely to have CVD compared with matched individuals with non-inflammatory chronic kidney diseases [16]. High-dose GCs have multiple metabolic effects leading to increased cardiovascular risk beyond hypertension and diabetes, including dyslipidaemia and weight gain, and are likely to be involved in this excess risk [7]. Weight gain can be considerable and persistent; 20% of patients gain over 10 kg and maintain this weight for over 12 months [17].

GC dosing has not been subjected to randomized trials, although recently initiated studies, most notably PEXIVAS (plasma exchange and glucocorticoid dosing in the treatment of ANCA-associated vasculitis) (http://clinicaltrials.gov/ct2/show/NCT00987389) and CLEAR (C5aR inhibitor on leukocytes exploratory ANCA associated renal vasculitis) (http://ir.chemocentryx.com/releasedetail.cfm?ReleaseID=811237), have specifically targeted GC dose reduction as a laudable principal outcome. The PEXIVAS trial has completed more than half of a recruitment target of 500 patients, and includes a reduced GC exposure arm. The CLEAR study of a novel orally available C5a receptor antagonist has completed two

sequential GC reduction steps with no loss of efficacy signal, and is now recruiting to a completely GC-free arm, the first time this has ever been attempted in an AASV trial. These trials will be reporting within a few years and results are eagerly awaited.

INFECTION RISK

Infection is one of the commonest adverse events leading to death and morbidity in AASV patients. Overall, 26–31% patients with AASV develop serious infections requiring hospital admission, up to one-third of which affect the respiratory tract [12, 18]. The burden of infection is greatest during remission induction, reflecting the intensity of immunosuppression. Advancing age not only increases the risk of infection, but also the resulting morbidity and mortality [19]. Leukopenia and deteriorating renal function are also associated with infections [19, 20]. Immune dysfunction induced by AASV therapy, including B-cell and T-cell depletion, aberrant immune-cell function and reduced immunoglobulin levels, also predisposes to infections [7]. Immunization is an attractive prophylaxis strategy, although no clear evidence exists that all patients with AASV will have an adequate response to vaccination, and no appropriate trials have addressed vaccination efficacy in patients with chronic autoimmune inflammatory diseases in general. Case series suggest that vaccination is safe and does not precipitate disease flares in patients with AASV [21–23]. Vaccination should be avoided during B-cell depletion therapy with rituximab, as this treatment consistently impairs humoral responses to immunization with influenza, pneumococcus and tetanus [24, 25]. Furthermore, live attenuated vaccines could lead to severe infections in immunocompromized patients, hence should not be used whenever possible [21–23].

Bacterial infections are frequently reported in patients receiving treatment for AASV (up to 62% of major infective episodes), including pneumonia (39% of all infections), cellulitis and generalized septicaemia [12]. Common respiratory pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* [26, 27]. Patients with GPA have a particularly high prevalence of *S. aureus* colonization of the upper respiratory tract [28], which is the most important risk factor for *S. aureus* septicaemia [18]. Infection with *Pneumocystis jiroveci (PCJ)* (previously *Pneumocystis carinii*) has an incidence of 0.8–12% in patients with AASV, with the lower end of this range reflecting the era of consistent co-trimoxazole prophylaxis. In the first year following diagnosis, 3% of patients recruited to four EUVAS trials developed PCJ [9, 29–31]. The clinical course of *P. jiroveci* infection is more acute and virulent in AASV than in HIV-related disease, with a higher mortality of up to 64% [32].

Viral infections accounted for 35.8% of all major infectious episodes in a long-term study [12]. Reactivation of varicella zoster virus is seen in 13–24% of patients with AASV which, although not life-threatening, causes considerable morbidity from post-herpetic neuralgia [12, 33]. Advanced age, female sex, immunosuppression and poor renal function are risk factors for varicella zoster virus reactivation [34]. How reactivation relates specifically to immunosuppression remains unclear. The results of a study published in 2005 suggested that most infections with varicella zoster occurred after the switch to maintenance therapy [35]; however, in historic reports, reactivation was linked to the immunosuppression intensity, with 4 infections per 100 patient-years in untreated individuals, a 10-fold increase in those on daily or alternate-day GC or daily CYC alone, and a 20-fold increase in concurrent GC and CYC use [26]. Although it is a live vaccine, the expert consensus from the Advisory Committee on Immunization Practices (ACIP) recommended that herpes zoster vaccine may be administered to patients when treated with (i) short term GC therapy (<14 days) (ii) low to moderate doses of GC (<20 mg/day of prednisolone or equivalent) (iii) long-term alternate day treatment with low to moderate dose of systemic GC (iv) or monotherapy with methotrexate (<0.4 mg/kg/week) or azathioprine (<3.0 mg/kg/day) [36]. Reactivation of latent cytomegalovirus infection is less frequent in patients with AASV than in recipients of solid-organ transplants, and accounts for only 7.5% of major infectious episodes in patients with AASV in long-term follow-up studies [12].

CONTEMPORARY IMMUNE MODULATING AGENTS: DISAPPOINTING REDUCTION OF INFECTION RISK?

Rituximab was initially used widely and successfully in the treatment of oncologic, haematologic and rheumatologic disease without significant increase in infection risk [37, 38]. It is as effective as CYC-based regimens when used as induction treatment and may be superior in relapsing disease [39, 40]. Rituximab was thought to be an opportunity to reduce the cumulative dose of CYC and avoid maintenance immunosuppression, reducing side effects such as leucopenia and infection. However, both the RAVE [40] and RITUVAS [39] trials showed no reduction in early severe adverse event rates, with similar mortality rates as CYC-based regimens. The French Vasculitis Study Group recently reported that approximately one in four rituximab-treated patients developed severe adverse events—12 had serious infections including pneumococcal meningitis and aspergillosis, leading to 4 deaths [41]. Current guidelines now recommend that patients should have their vaccination status assessed, along with careful exclusion of viral hepatitis prior to treatment. Reactivation of various latent viral infections, including hepatitis B, has been associated with rituximab therapy in several settings [42–44]. In addition, there is emerging evidence that the use of rituximab may increase the risk of PCJ infection [45]. Although PCJ is generally associated with a defect in T cell-mediated immunity, B cells have been proven to play an important role in the host defence against this infection, not only by the production of antibody, but also by regulating the quality of the T-cell-mediated immune response [46]. We suggest continuing prophylaxis until B cells have reconstituted, but acknowledge that there is controversy about this. Perhaps one of the most feared complications is progressive multifocal leucoencephalopathy (PML), a rare demyelinating infection of the central nervous system caused by JC

papovavirus, resulting in irreversible neurological damage and death. Cases of PML have been reported in patients receiving rituximab for the treatment of lymphoproliferative disorders [47]. Although similar cases have not been observed in AASV, the theoretical risk remains and clinical vigilance is required during follow-up. Late-onset neutropenia (LON), which is usually self-limiting, occurs in approximately 6% of patients with autoimmune disease treated with rituximab. The risk of infection associated with LON is unknown in AASV patients but in a review of retrospective case series, infection only occurred in 16.9% of affected patients and most were mild with prompt resolution [48].

MALIGNANCY

The overall incidence of cancer in treated AASV patients was previously reported as being 1.6–2.4 times higher than that of general population, with bladder cancer, non-melanoma skin cancer (NMSC), leukaemia and lymphoma being the most commonly reported malignancies [4, 26, 49, 50]. However, the extent of this risk is dependent on the organ affected, with a 33-fold increased risk in bladder cancer. This reflects the extensive use of high-dose CYC during the 1970s and 1980s [51]. The standardized incidence ratio (SIR) for malignancy in EUVAS trials (1995–2007) was 1.58 (95% CI 1.17–2.08) for cancers at all sites and 1.30 (95% CI 0.90–1.80) for cancers at all sites excluding NMSC [52]. The apparent lower risk of malignancy compared to previous studies could be explained by the use of the modern CYCLOPS protocol, which allows administration of approximately one-eighth of the total cumulative CYC dose of the 2-year Fauci regimen. Indeed, among all the cancer sites, NMSC was the only one to demonstrate a statistically significant increase in incidence. Longer follow-up data are required to confirm this finding as the median duration of follow-up of these patients was only 5 years and a French study suggests that the increased risk of urinary tract cancer remains a concern [53]. Current findings support the need for regular skin surveillance and ultraviolet radiation protection in AASV patients. Of note, malignancy has not been reported as an important risk when using rituximab [54].

INFERTILITY

CYC primarily affects the function of granulosa cells of the primordial follicles in the ovary, suppressing oestrogen production and stimulating gonadotropin release, which increases the number of follicles that are susceptible to CYC toxicity and ultimately pre-maturation and depletion of the ovaries [55]. The cumulative dose of CYC and the age of initiation of treatment are the most important predictors of ovarian failure [56, 57]. Data from lupus nephritis suggest that a total CYC exposure of 14–20 g causes infertility in >50% of women aged over 32 years, with lower risk in younger women [58]. Long-term therapy with CYC in patients with GPA was previously reported by the NIH to result in infertility rates in between 40 and 57% in women [26]. CYC also directly affects sperm

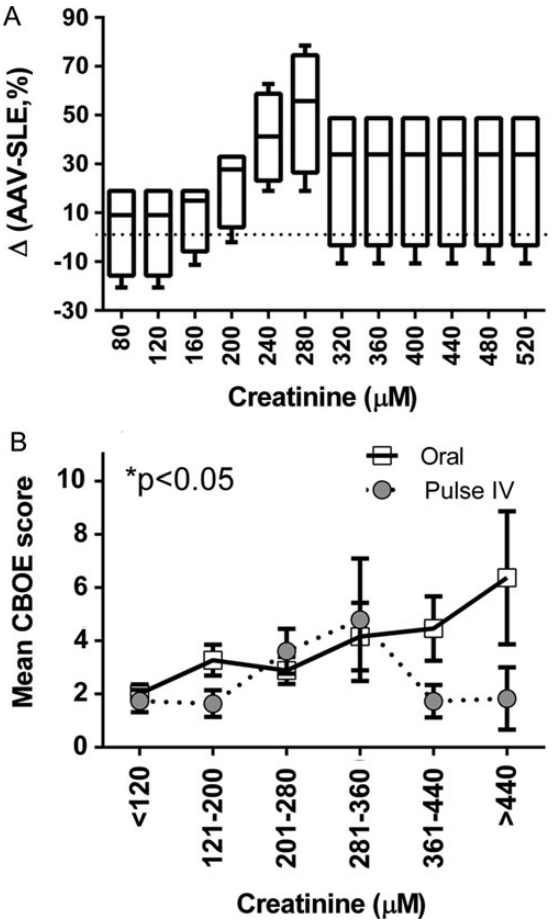

FIGURE 1: (A) In silico comparison of predicted dosing of CYC using NIH SLE and CYCLOPS regimens across a range of ages and renal dysfunction. Those with moderate renal dysfunction receive a relative excess of CYC. (B) Comparison of observed combined burden of adverse events (CBOE) score across a range of kidney dysfunctions in EUVAS trial participants receiving the CYCLOPS regimen and those receiving daily oral CYC (not dose reduced for kidney failure). The CBOE score was lower in the CYCLOPS regimen recipients, except in those with a creatinine level between 200 and 360 μM.

production in men but there is more potential for recovery by the generation of new sperm forming cells when CYC is withdrawn. More recent EUVAS trial long-term follow-up reported gonadal failure in 4.1% of patients, although this was not a priori outcome [11]. Rituximab is not known to reduce fertility and is therefore an important alternative induction agent in young AASV patients wishing to preserve fertility.

RATIONAL CYC DOSING IN AASV

CYC is an inactive prodrug, converted via hepatic enzymes to active alkylating metabolites including 4-hydroxycyclophosphamide, aldophosphamide, acrolein and phosphoramide mustard. Although renal function is generally thought to be less important than liver function in determining CYC exposure, with only small reductions in dose in kidney failure recommended in most published guidelines, empirical data

from numerous clinical studies point to reduced GFR as being the pre-eminent predictor of adverse events in CYC-treated patients. This is presumably due to accumulation of kidney excreted active metabolites, most notably acrolein, and provides a strong rationale for selective CYC dose reduction, as employed in the latter EUVAS studies [59]. This approach identifies arbitrary age (> 60 and 70 years) and GFR cut-offs (creatinine > 300 μmol/L), which has the desired effect of reducing CYC exposure in those at high risk, but introduces relative overdosing in middle-aged patients with moderate renal dysfunction. A post-hoc analysis of EUVAS trial data suggests that this relative overdosing is mirrored by excess adverse events (Figure 1). Modelling of CYC dosing using empiric EUVAS trial data demonstrates a hyperbolic relationship between GFR and adverse events, with an inflection point at 25 mL/min, and a linear relationship between age and adverse events. Mapping these curves onto CYC doses allows for the development of a nomogram that smoothly adjusts CYC dose for age and GFR [60], which is currently being tested in clinical practice. More recently, Joy and colleagues demonstrated that the pharmacokinetics of CYC and its active metabolites (4-hydroxycyclophosphamide) in patients with glomerulonephritis are influenced by clinical and genetic covariates (polymorphisms in CYP2B6 and ABCB1) [61]. Patients with hypoalbuminaemia and proteinuria had reduced exposure to 4-hydroxycyclophosphamide, potentially blunting the therapeutic response. There is currently considerable research interest in cyclophosphamide (and rituximab) pharmacogenomics with a view to developing individualized therapy.

CHANGING STRATEGIES—EMPHASIS ON PREVENTION

Greater attention is now placed on prevention as part of the overall treatment strategy to minimize potentially preventable adverse events. The British Society for Rheumatology, British Health Professionals in Rheumatology and EUVAS guidelines for management of AASV advocate

(i) Co-trimoxazole prophylaxis against *Pneumocystis jiroveci*
(ii) Vaccination against pneumococcus and influenza
(iii) *Staphylococcal aureus* eradication with long-term nasal mupirocin
(iv) Robust cardiovascular and thromboembolic risk assessment
(v) Tuberculosis screening

A Delphi exercise sponsored by the UKIVAS group in the UK to define in more detail practical approaches is currently underway and will report by the end 2014.

CONCLUSION AND FUTURE PERSPECTIVES

Rapid diagnosis with early initiation of intensive induction treatment has revolutionized AASV treatment, improving survival and limiting end-organ damage. Careful supervision of therapy, especially with CYC and high-dose GC, has led to reductions in severe adverse events over the last 20 years, and in late treatment-related toxicity. This may be improved further by the availability of rituximab as an alternative to CYC. Glucocorticoid avoidance, delayed treatment response and high relapse rates are important components of the unmet need of current vasculitis therapies. Due to the rarity of disease, improving treatments will remain a challenge until the pathogenic mechanisms and predictors of damage are better understood to allow a personalized approach to treatment.

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CONFLICT OF INTEREST STATEMENT

None declared.

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