A COST EFFECTIVENESS ANALYSIS OF WEEKLY COMPLETE BLOOD COUNT MONITORING FOR LEUKOPENIA IN PATIENTS WITH GRANULOMATOSIS WITH POLYANGIITIS (GPA) ON CYCLOPHOSPHAMIDE

By

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Submitted in partial fulfillment of the requirements

For the degree of Master of Science

Clinical Research Scholars Program

CASE WESTERN RESERVE UNIVERSITY

August 2011

CASE WESTERN RESERVE UNIVERSITY

SCHOOL OF GRADUATE STUDIES

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DEDICATION

To my parents Ashok and Arati Khasnis, my wife Rupali, sons Om and Shree, and all my teachers

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LIST OF ABBREVIATIONS

ANC	Absolute Neutrophil Count
ANCA	Anti-neutrophil cytoplasmic antibody
AZA	Azathioprine
BVAS	Birmingham Vasculitis Activity Score
CBC	Complete Blood Count
CEA	Cost-Effectiveness Analysis
CYC	Cyclophosphamide
DVT	Deep Venous Thrombosis
GPA	Granulomatosis with Polyangiitis
ICER	Incremental Cost Effectiveness Ratio
MMF	Mycophenolate Mofetil
MPO	Myeloperoxidase
MTX	Methotrexate
PR3	Proteinase-3
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjusted Life Years
QoL	Quality of life
RTX	Rituximab
WBC	White Blood Cell
WG	Wegener's granulomatosis

A Cost Effectiveness Analysis Of Weekly Complete Blood Count Monitoring For Leukopenia In Patients With Granulomatosis with Polyangiitis (GPA) On Cyclophosphamide

Abstract

By

ATUL ASHOK KHASNIS

OBJECTIVE: To assess the cost-effectiveness of weekly compared to monthly white blood count (WBC) monitoring in patients with severe granulomatosis with polyangiitis (GPA) receiving oral cyclophosphamide (CYC).

METHODS: The two CBC monitoring approaches for surveillance of leukopenia and its consequences were compared using a decision analysis model. The prevalence of leukopenia, infections, and outcomes were obtained from an existing registry and published reports. Costs were in dollars (2010) and effectiveness as quality-adjusted life-years (QALYs) gained.

RESULTS: The expected utility of weekly CBC monitoring of these patients for leukopenia is 18.74 QALYs versus 18.52 QALYs with monthly CBC. The expected gain is 0.22 QALYs and incurs $489 lower cost per patient. The weekly CBC strategy mostly dominated the monthly CBC strategy.

CONCLUSION: Weekly CBC monitoring is cost-effective for prevention of severe leukopenia and severe infections in patients on CYC for severe GPA.

Background

Wegener's granulomatosis was first described as a disease entity by Klinger in 1931[1] and then as a case series of three patients by Friedrich Wegener in 1936[2]. In 2011, the name was officially changed to Granulomatosis with polyangiitis (GPA)[3] in an attempt to remove its eponymous association and replace it with nomenclature more suggestive of its histopathologic features. It is a serious multisystem disease characterized by inflammation of small and medium sized blood vessels in different organ systems, which may result in significant organ damage as a consequence of the inflammation itself or as a result of tissue ischemia. Almost any organ can be involved in patients with GPA, but the triad of upper respiratory tract, lower respiratory tract and kidneys has been classically described. Vascular inflammation can have serious consequences resulting from tissue ischemia. Granulomatous as well as non-granulomatous inflammation and necrotizing as well as non-necrotizing tissue pathology has been well described in biopsies of patients with GPA. In 1966, Carrington and Liebow[4] coined the term "limited forms" of GPA to describe patients who did not have renal involvement from GPA. The use of this terminology however is fraught with the risk of deceptively conveying a more "benign" form of GPA, which is not true as severe "limited" organ involvement may be organ-threatening or life threatening in an individual patient. It is therefore most prudent to characterize GPA based on the extent and severity of organ involvement in an individual patient rather than labeling it as "limited GPA" or "generalized GPA". The diagnosis of GPA is best made as a combination of clinical features, supporting serology (anti-neutrophil cytoplasmic antibody (ANCA)), tissue biopsies as indicated and supporting radiologic findings.

Untreated GPA has a dismal prognosis, with patients in the 1950's experiencing a median survival of 5 months after diagnosis[5]. The introduction of glucocorticoids (GC) in the 1950's for inflammatory arthritis[6] was followed by their use in patients with GPA. In a retrospective review, the use of GC extended the median survival of patients with GPA to 12 months[7]. In 1973, the introduction of combination therapy with cyclophosphamide (CYC) and GC represented a paradigm shift in the approach to treatment of patients with GPA. The use of oral CYC and high dose GC resulted in achievement of disease remission in over 90% patients enrolled in the study conducted by Fauci et al.[8] at the National Institutes of Health (NIH). This led to the use of a treatment strategy of initiating treatment for patients with severe GPA with CYC and high dose GC followed by gradual taper and eventual discontinuation of the GC over the following months and continuation of CYC as maintenance therapy. This resulted in long-term exposure to CYC. The appreciation of toxicities (infection, hematologic, bladder, malignancy) resulting from long term CYC therapy was a sobering experience which led to the concept of limiting exposure to CYC for indicated periods of time and transitioning to a maintenance immunosuppressive medication with a safer risk profile such as methotrexate (MTX), azathioprine (AZA), or mycophenolate mofetil (MMF). The most recent addition to the therapeutic armamentarium for treatment of GPA is rituximab (RTX), a monoclonal antibody targeted against B cells that have a role in the pathogenesis of this disease.

Since the first systematic trial using CYC in the management of patients with GPA, leukopenia (a reduction in white blood cell count) has been reported as a common occurrence. In 1970, Morley et al. published a study producing cyclic neutropenia in dogs using CYC in an attempt to create an animal model of the disease[9]. However,

many clinical trials of patients with GPA using CYC have not consistently incorporated a formal definition of leukopenia or management strategy for leukopenia into their trial protocol or formal publication of the trial results. Mechanistically, the link between leukopenia and infection is likely a combination of the broad qualitative and quantitative effects of CYC on multiple cell lines of the WBC lineage such as neutrophils and lymphocytes[10, 11]. The NIH trial by Fauci et al.[8] used a WBC count of less than 4000/mm^3 as the criteria for leukopenia. Since neutropenia is a stronger determinant of incipient serious infection and sepsis, some studies specify the definition of leukopenia as a WBC count of < 3000/mm^3 or an absolute neutrophil count (ANC) of less than 1500/mm^3 (severe neutropenia defined as ANC less than 500/mm^3). These criteria are based on early studies of infections in patients with acute leukemia[12]. For the purposes of this study, leukopenia was defined as WBC count less than 4000/mm^3 without accompanying ANC levels, as the WBC differential was not available accompanying multiple WBC measurements. To further identify patients with severe leukopenia, a cutoff of WBC < 2000/mm^3 was used. As mentioned earlier, due to the non-availability of ANC, neutropenia was not used for definition purposes.

Cyclophosphamide (CYC) is an alkylating agent with immunosuppressive properties. It is used in the management of severe manifestations of systemic autoimmune diseases such as systemic lupus erythematosus (SLE) and the vasculitides including but not limited to Granulomatosis with Polyangiitis (GPA) [previously known as Wegener's granulomatosis (WG)], microscopic polyangiitis (MPA), Churg Strauss syndrome (CSS) and polyarteritis nodosa (PAN). It may be given by the intravenous (IV) (500-1000 mg/m^2 body surface area usually given at monthly intervals) or oral route (2 mg/kg given daily). The oral route is used more commonly in the

management of the vasculitides. The introduction of CYC into the therapeutic regimen of patients with GPA was a major advance in prolonging survival in these patients. However, CYC use is associated with considerable toxicity and therefore warrants close monitoring. A major toxicity of CYC is a decrease in white blood cell (WBC) count (leukopenia) accompanied by decreased lymphocyte counts (lymphopenia) and decreased neutrophil count (neutropenia). Severe neutropenia (absolute neutrophil count < 500/mm^3) may predispose to life-threatening infectious complications such as sepsis. Although there are some guidelines provided by the American College of Rheumatology (ACR) regarding monitoring of patients on CYC for leukopenia, these are not evidence-based. The guidelines also provide no recommendations about the threshold for or type of intervention based on the presence or severity of leukopenia or neutropenia. The recommended monitoring for leukopenia in these patients is a complete blood count (CBC) with a differential WBC count. The ACR patient encounter template uses a CBC with differential WBC count every 1-2 wks with changes in dosage, then every 1-3 months.[13] The 2009 European League against Rheumatism (EULAR) guidelines for the management of medium and small vessel vasculitides recommends a CBC every 1-3 months to monitor for drug toxicity.[14] However, in studies previously performed at the National Institutes of Health (NIH) and now at the Center for Vasculitis Care and Research at the Cleveland Clinic, it is practice to continue to check CBC weekly for the duration of time that patients are on CYC. This approach is also not strictly evidence based. Given that neither strategy mentioned above is evidence based, this study was undertaken to compare these two monitoring strategies (weekly versus monthly CBC) regarding the cost-effectiveness of each approach.

Pharmacology of Cyclophosphamide (CYC)

CYC is well absorbed orally. The drug is activated by a hepatic microsomal CYP2B[15] to 4-hydroxycyclophosphamide, which is in a steady state with another metabolite, aldophosphamide. Pharmacokinetic studies from the oncology literature have shown that the rate of metabolic activation of CYC exhibits significant variability between patients and increases with successive doses in high-dose regimens, but appears to be saturable above infusion rates of 4 grams/90 minutes and concentrations of parent compound above 150 M.[16] 4-Hydroxycyclophosphamide may be oxidized further by aldehyde oxidase, either in liver or in tumor tissue, and perhaps by other enzymes, yielding the inactive metabolites carboxyphosphamide and 4-ketocyclophosphamide. The active CYC metabolites such as 4-hydroxycyclophosphamide and aldophosphamide, are carried in the circulation to target cells where aldophosphamide cleaves spontaneously, generating phosphoramide mustard and acrolein. Phosphoramide mustard is responsible for cytotoxic effects of CYC. CYC undergoes hepatic and extra-hepatic metabolism and is eliminated renally (68%); thus dose adjustments are necessary in patients with hepatic and renal dysfunction. Urinary and fecal recovery of unchanged CYC is minimal after intravenous administration. Maximal concentrations in plasma are achieved 1 hour after oral administration, and the half-life of parent drug in plasma is about 7 hours.

The immunosuppressive effects of CYC are observed after 2-3 weeks of therapy and the nadir of the WBC count is usually occurs 7-14 days after the dose with recovery by 21-28 days. To monitor the trend of WBC counts, in the paper by Langford[17], there is a suggestion to check CBC on day 7, 10, 14, 21 after the CYC dose. CYC should be held for a WBC count $\leq 3500/mm^3$ and restarted after the WBC count improves to $\geq$

4000/mm^3. It is emphasized that even after achieving a steady CYC dose in an individual patient; the CBC should be followed closely in anticipation of cytopenias that may occur later from a cumulative effect of CYC on the bone marrow. GPA is a relapsing illness and therefore patients may require retreatment with CYC for severe relapses, which may lead to a subclinical compromise of the bone marrow reserve for hematopoiesis.

The relationship between CYC and leukopenia

Leukopenia is commonly observed with CYC therapy. Fauci et al.[8] (1973) mention that, "leukopenia to a greater or lesser degree is an inevitable complication of cyclophosphamide therapy". Leukopenia typically occurs on days 10-14 after oral cyclophosphamide therapy. Therefore the WBC count reflects the effects of CYC dosing over the previous week and the dose of CYC accordingly if indicated to prevent worsening WBC counts in the coming week. Patients may also experience leukopenia from CYC more easily if they have been subjected to multiple previous courses of CYC therapy of if they have been exposed to CYC for prolonged periods in the past. Leukopenia may occur with other immunosuppressants used to treat patients with GPA, but in reviewing the literature it is difficult to assess this effect if it happens shortly after transitioning from CYC as the effects of CYC may last for months making it difficult to implicate the other immunosuppressant. In the detailed study of the effects of CYC on leukocyte kinetics and susceptibility to infection in patients with GPA, Dale et al.[18] noted a decrease in mean WBC count from 11117/mm^3 to 4203/mm^3. The mean neutrophil, monocyte and lymphocyte concentrations were all reduced compared to pretreatment and normal levels. Granulocyte kinetic studies in three patients with active disease before therapy with

glucocorticoids or CYC revealed that the total blood granulocyte pools and granulocyte turnover are increased; these returned to the normal range with treatment.

The duration of leukopenia has also been shown to be a significant factor regarding the risk of infection as documented in the oncology literature[19]. This seems logical, as transient neutropenia likely does not portend a risk of infection comparable to sustained neutropenia over a period of days. This is an important consideration to the present study as it again emphasized that if WBC counts are not measured frequently enough and consequently not acted upon, the opportunity to intervene may be lost and the risk of infection subsequently significantly increased. None of the studies available in literature report the duration of severe leukopenia in the context of CYC use in patients with GPA who received oral CYC limiting our ability to make inferences regarding this factor in our analysis or discussion. In our database, only two patients appeared to have sustained leukopenia (as defined by WBC counts < $2000/mm^3$ on two serial counts one week apart). Both these patients had been previously treated with CYC.

One other factor to consider regarding the etiology of leukopenia is bone marrow function in patients with GPA. In the same immunology study by Fauci et al.[18] mentioned earlier, bone marrow granulocyte reserve as measured by response to etiocholanolone was abnormal in five of seven patients even before starting CYC therapy and decreased further with therapy. This suggests a possible abnormal bone marrow granulocyte quantitative precursor or maturation reserve that may be present in patients with GPA as a background contributor to the observed leukopenia after initiating therapy with immunosuppressant medications.

The other major factor is concomitant therapy such as glucocorticoids. Patients who are started on CYC for acute severe GPA will invariably receive high dose glucocorticoids (oral or initially parenteral followed by oral) as standard of care, which can confound the quantitative as well as immunologic assessments of WBC in patients with GPA. The studies conducted by Fauci et al. mentioned above were done in a small number of patients but offer clear information about their treatment status. This information on treatment naïve patients is very difficult to obtain today given that almost all patients receive prompt treatment with glucocorticoids as soon as the diagnosis is made which interferes significantly with the ability to perform immunologic studies. Glucocorticoids decrease circulating lymphocytes, eosinophils, monocytes and basophils by redistribution from the periphery whereas they increase circulating neutrophils as a consequence of increased release from the bone marrow, decreased exodus from the circulation, and increased demargination from the vessel walls. Therefore initial high dose glucocorticoid therapy may actually theoretically mask the effects of CYC and WBC counts need to be watched closely as glucocorticoids are being tapered.

Severe leukopenia and potential outcomes

Severe infection is the most dreaded consequence of leukopenia (neutropenia). In the study of patients with acute leukemia at the NIH by Bodey et al.[12], 52 patients were studied. Absolute granulocyte (neutrophil) counts were divided as 100-500 cells/mm^3, 500-1000 cells/mm^3, 1000-1500 cells/mm^3, 1500-2000 cells/mm^3 and > 2000 cells/mm^3. The relationship between granulocyte levels and all types of proven infection were noted to be similar. Fever without proven infection was not related to the granulocyte level. At granulocyte count < 100/mm^3, 53% patient days were spent

with an infection. An inverse relationship was noted between the granulocyte count and incidence of infection up to a granulocyte count of 1500/mm^3 after which the relationship is flat suggesting no further reduction in risk of infection. This paper has served an important contributor for the definition of severity of leukopenia used in several studies and also for the Common Terminology Criteria for Adverse Events (CTCAE)[20] devised by the National Institutes of Health (NIH) and the National Cancer Institute (NCI) for the since this paper was published.

Severe leukopenia constitutes only one of the risk factors for infection and potentially severe infection, but it is by no means the only mechanistic link in this causal pathway. However, it is the easiest to measure practically and is standardized across most laboratories as compared to tests to assess leukocyte function. The amelioration of leukopenia is also associated with mitigation of the risk of infection. It has been well demonstrated that CYC has effects beyond quantitative depletion of WBC such as effects on immunoglobulin production and leukocyte mobility. These functional alterations are not routinely assessed in clinical practice for logistic reasons. Therefore, although measuring WBC counts only allows us to assess one facet of the effects of CYC on leukocytes, it is a practically and economically feasible accepted testing strategy. It is important to remember that patients during the induction phase of treatment for GPA are also on high doses of glucocorticoids, which have qualitative and quantitative effects on leukocytes, and this has to be factored into the analysis. In the CCF GPA database, the patients with severe leukopenia who experienced severe infection were on a median prednisone dose of 35 (Intequartile range 30 – 40) mg daily which would be considered a moderately high dose of prednisone.

In the study by Little et al.[21], it is noteworthy that the reported mortality within the first year in patients with Wegener's granulomatosis and attributable to infection is 50% compared to 14% from active vasculitis. Half of these infections occurred in the first two months, which is the period when patients are most likely to be on a combination of CYC and high dose glucocorticoids as induction therapy for the vasculitis. Luqmani et al.[22] found that patients with GPA have a 9-fold increased risk of death in the first year of disease, attributable to three main factors: infection, active vasculitis and renal failure. Between 1 and 8 years the risk was found to be the lowest, although higher than the control population and beyond eight years, there is an unexplained increased mortality.

Background literature review

CYC is an effective treatment for severe manifestations of the vasculitides. Since the purpose of this analysis is to study monitoring of CBC for CYC toxicity in patients with the primary systemic vasculitides, the literature review (Table 1.) was restricted to studies reporting oral CYC use in patients with these diseases. CYC was first used for the treatment of GPA in the 1960s. The use of CYC was a major advance in the treatment of patients with GPA.[8,23, 24]

In 1973, Fauci et al.[8] reported the use of CYC in 18 patients with GPA. The patients received oral CYC at 1-2 mg/kg daily. Three patients with severe disease received IV CYC at 2-4 mg/kg daily. Per protocol, the initial dose was maintained for 10 days to 2 weeks. If no effect was observed, the dose was increased by 25 mg/d and again maintained for 10 days to 2 weeks. This dose escalation was continued till clinical

response was seen or the WBC count dropped to < 3000/mm^3. Four patients received CYC as their only treatment while others were switched over to a maintenance agent as remission was achieved. Three patients died before the institution of immunosuppressive therapy. In the clinical course of 12 patients tabulated in the paper, no patient is reported to experience a serious infection or experience mortality from sepsis. The paper mentions "leukopenia to a greater or lesser degree is an inevitable complication of cyclophosphamide therapy", but no details are available regarding the development of severe leukopenia in the cohort in this study.

In a study of 85 patients with GPA followed over 21 years, Fauci et al.[24] successfully induced remission in 93% patients using a regimen of oral CYC (induction dose of 2 mg/kg daily for severe disease and 4-5 mg/kg daily for fulminant disease for the first few days) and prednisone (1 mg/kg daily for severe disease and 2 mg/kg/d for fulminant disease for the first few days). The investigators clearly state their aim to maintain a WBC count > 3000 – 3500/mm^3. To this end, they checked WBC counts on alternate days after starting CYC and then every 1-2 weeks after dose stabilization. They reported 1 patient with bacterial sepsis in their study. Nine episodes of herpes zoster were also reported in seven patients.

In the study by Cohen et al.[25], of 75 patients (18 with GPA and 16 with other primary systemic vasculitides) were treated with CYC and prednisone. There were 70 infections in the patients with GPA. CYC was associated with infection only in the presence of neutropenia (preceded 13 infections in nine patients- 12%). The total dose of CYC was 6.24 grams. 77% infections were bacterial (70% Gram negative), 10% were viral, 4.3% were fungal infections. Pneumonia was most common followed by

urinary tract infection. 4 patients died; 3 had WBC counts < 2000/mm^3. Per protocol, the CYC was stopped if two successive neutrophil counts were < 2000/mm^3.

The NIH study[26] reported experience with CYC use over a 24-year period in 133 patients with GPA and reported improvement in 91% and remission in 75% patients. However, 13% patients died from the disease or complications of therapy. The induction regimen consisted of CYC given orally at 2 mg/kg along with prednisone 1 mg/kg daily. After a month, the prednisone was tapered using an alternate day schedule such that it was tapered to off over 6-9 months if the patient continued to stay in remission. CYC was continued for at least a year after achieving remission and then tapered by 25 mg every 2-3 months. 73 patients (46%) experienced 140 serious infections over 1229 patient years (0.11 infections per patient year) – pneumonia (57 episodes (39%), skin (38 episodes (26%), bacterial or fungal sepsis (13 episodes, (9%)). The overall mortality from infection in this cohort was 3%.[26] There is no mention of the WBC or ANC mentioned in patients who experienced serious infections. There is also no reference to the monitoring strategy for leukopenia/ neutropenia in these patients while on CYC.

Adu et al.[27] compared IV CYC (n = 24) or oral CYC (n = 30) and prednisone in patients with primary systemic vasculitides in a randomized fashion. 13/30 patients in the oral CYC group experienced leukopenia (actual WBC count not available) and the number of infections during follow up was 1.66/patient (not statistically significantly different from the IV CYC group). Urinary tract infections were most common followed by chest infections. Two patients in the IV CYC group died from septicemia. No monitoring strategies or protocol for adjustment of CYC dose for

leukopenia are mentioned in the paper.

In the study by Guillevin et al.[28], 52 patients with newly diagnosed GPA were randomly assigned to receive either prednisone plus IV CYC (group A) or prednisone plus oral CYC (group B) as first-line treatment. CYC was given for at least 1 year and was then progressively tapered and discontinued. 27 patients were in group A and 23 in group B. The goal of CYC therapy in this study was to induce a WBC count < 3000/mm^3. At 6 months, 24 group A patients (88.9%) were in remission, versus 18 group B patients (78.3%). At the end of the trial, 18 group A patients (66.7%) and 13 group B patients (56.5%) were in remission. Infectious side effects were significantly more frequent in group B (69.6%) than in group A (40.7%) ($p < 0.05$). The incidence of *Pneumocystis carinii* pneumonia was higher in oral CYC-treated patients (30.4%) than in pulse CYC-treated patients (11.1%). Nine group A patients (33.3%) and 10 group B patients (43.5%) died.

Haubitz et al.[29] studied the efficacy and toxicity of IV CYC (0.75 gm/m^2) versus daily oral CYC treatment (2 mg/kg body weight) in a prospective, randomized, multicenter study in 47 patients with ANCA-associated vasculitis and renal involvement. The cumulative CYC dose was reduced by 57% in patients with intravenous pulse treatment (n = 22) compared with patients treated with daily oral therapy (n = 25). For patients on oral CYC, daily oral treatment was started at 1.5 mg/kg body weight daily and increased to 2 mg/kg body weight daily after 2 weeks provided that the leukocyte counts were >3,000/mm^3. If leukocyte levels were < 2500, the dose was reduced by 50%, and if the leukocyte counts dropped below 1500/mm^3, the drug was withheld until they increased above 2500/mm^3. For patients on IV CYC, the CYC dose was

adjusted to the leukocyte count, which was aimed at a minimum of 3000. If the leukocyte nadir was < 2500/mm^3, the dose was reduced by 0.25 gm/m^2. Sixty percent of the patients receiving daily oral CYC, but only 18% of the patients receiving IV pulse CYC, developed at least 1 episode of leukopenia (WBC < 3000) *(P* < 0.01). In all but 4 patients, lymphocyte counts were monitored monthly. Severe lymphopenia (< 400/mm^3) occurred in 86% of the patients with oral CYC administration and in 47% of the patients with IV pulse CYC administration *(P* < 0.01). Severe infections occurred in 10 patients receiving daily oral CYC; 3 died of sepsis (one also had ongoing disease activity). In the group receiving IV CYC, 3 patients developed severe infection and none died.

Langford et al.[30] studied the efficacy of oral CYC for induction followed by methotrexate (MTX) for maintenance of remission in 31 patients with GPA at the NIH. All patients were initially treated with oral CYC 2 mg/kg/day with prednisone 1 mg/kg/day. Per protocol, a CBC was checked every 1-2 weeks with the goal of maintaining a WBC count > 3000/mm^3 (neutrophil count > 1500/mm^3). Once satisfactory remission was achieved, the patients were transitioned from CYC to MTX with prednisone being tapered to off guided by disease activity. Using this strategy, disease remission was achieved in all patients in a median time of 3 months. Three patients on CYC experienced leukopenia requiring dose reduction, but none had a neutrophil count of < 1500/mm^3. Two patients experienced serious infection (pneumonia), but there were no deaths reported in this study.

In another large cohort of 155 patients with GPA from Germany[31], 142 (92%) were treated with CYC (137 oral CYC and 5 pulse IV). The patients were followed for a

median of 7 years. Concomitant therapy with daily prednisone at 1 mg/kg of body weight was started in all patients with a generalized course; the dosage was reduced to 5–10 mg/day within the first 3–6 months and then gradually tapered in steps of 1 mg/month. Under induction treatment, all patients experienced at least partial remission, 83 (54%) attaining complete remission. Fifty-six serious infections requiring hospitalization, mostly pneumonia or sepsis, were observed in 41 patients (26%). In 5 patients, serious infections (including 4 *Staphylococcus aureus* septicemia and 1 pneumonia caused by an unidentifiable organism) in addition to active GPA led to death. There is no mention of the WBC or absolute neutrophil count mentioned in patients who experienced serious infections. There is also no reference to the monitoring strategy for leukopenia/ neutropenia in these patients while on CYC.

In 2003, Langford et al.[32] published an extended (median 32 months) follow up study on 42 patients with GPA (an extension of their previous study[14]) initially treated with oral CYC 2 mg/kg/day with prednisone 1 mg/kg/day. Once satisfactory remission was achieved, the patients were transitioned from CYC to MTX with prednisone being tapered to off guided by disease activity. Using this strategy, disease remission was achieved in all patients in a median time of 3 months. All patients were able to stop prednisone at median 8 months. Leukopenia requiring dose reduction of CYC occurred in 4 patients.

In 2003, in the CYCAZAREM trial, Jayne et al.[33] studied 155 patients with a new diagnosis of generalized vasculitis and a serum creatinine of ≤ 5.7 mg/dl. All patients received at least three months of therapy with oral CYC and prednisolone. After remission, patients were randomly assigned to continued CYC therapy (n = 73, 1.5

mg/kg body weight daily) or a substitute regimen of azathioprine (n = 71, 2 mg/kg/day). Both groups continued to receive prednisolone and were followed for 18 months from study entry. CYC was discontinued if the patient had a WBC count < 4000/mm^3. Study assessments (clinical and laboratory) were performed after 0, 1.5, 3, 6, 9, 12, 15, and 18 months and at the time of relapse, if it occurred. 55% patients (85/155) had at least one episode of neutropenia. Severe or life-threatening events occurred in 15 patients (10%) during the remission-induction phase, in 8 patients in the azathioprine group during the remission-maintenance phase (11%), and in 7 patients in the CYC group during the remission-maintenance phase (10%). Of 33 infections, 17 (52%) were associated with concurrent neutropenia. There were eight deaths (5 %); 7 during the first 3 months.

In 2004, Langford et al.[34] published their experience with using mycophenolate mofetil (MMF) as a maintenance agent after initial use of oral CYC for induction of remission in 14 patients with GPA. All patients were initially treated with oral CYC 2 mg/kg/day with prednisone 1 mg/kg/day. Per protocol, a CBC was checked every 1-2 weeks with the goal of maintaining a WBC count > 3000/mm^3 (neutrophil count > 1500/mm^3). Once satisfactory remission was achieved, the patients were transitioned from CYC to MMF with prednisone being tapered to off guided by disease activity. Remission was induced in all patients at median 3 months. Two patients required a dose reduction in CYC for leukopenia; however none had a neutrophil count < 1500/mm^3.

Harper et al.[35] performed a retrospective, single centre, sequential cohort analysis of elderly patients (age > 65 years) with ANCA associated vasculitides (233 consecutive

patients from 1990 and 2000). WBC counts were checked at each clinic visit (the frequency of follow up is not mentioned in this retrospective study). All patients received 2 mg/kg oral CYC until remission was achieved and prednisolone 60 mg/day tapering to 7.5 mg/day by 6 months. 25% dose reductions of CYC were made for those aged over 65 yr or those who developed leukopenia (WBC count < 4000/mm^3). The risk of death was increased in those who developed an infection requiring hospitalization (OR 1.58). Older patients were more likely to develop infection (OR 1.9). The risk of an infection in those who developed leukopenia was increased (OR 1.75). Leukopenia was more likely to occur when patients were receiving CYC (OR 1.24). Severe renal disease (creatinine >400 μmol/l) also increased the risk of leukopenia (OR 1.43). There was no difference in the types of infection that older patients developed: 20 patients in total developed an opportunistic infection, only one patient developed *Pneumocystis carinii* pneumonia.

The GPA Etanercept Study study[36] was a randomized, placebo-controlled trial to evaluate etanercept for the maintenance of remission in 180 patients with GPA. In addition to etanercept or placebo, patients received standard therapy (glucocorticoids plus CYC or methotrexate). The starting daily dose of prednisone ranged from 0.5 to 1.0 mg/kg body weight. At the investigators' discretion, patients with severe GPA could receive 1 gm of methylprednisolone per day three times before starting prednisone. Patients with limited disease initially received 0.25 mg/kg methotrexate per week, and the dose was increased to a maximum of 25 mg per week. Patients with severe disease received CYC 2 mg/kg per day. Of the 174 patients who could be evaluated, 126 (72.4 percent) had a sustained remission, but only 86 (49.4 percent) remained in remission for the remainder of the trial. 49.4 % patients in each group had

infections that ranged in severity from moderate to fatal. One patient in each group died from sepsis.

DeGroot et al. (EUVAS group)[37] randomized 100 patients without critical organ involvement from GPA to CYC 2 mg/kg/day orally (maximum 150 mg/d) (n=49) or methotrexate 20-25 mg/week (n=51). Per protocol, the CYC dosage was reduced by 25 mg/d in patients aged > 60 years and withdrawn if the WBC count was < $4000/mm^3$. Once the patients were in remission, the CYC was reduced to 1.5 mg/kg/day until month 10 and then tapered and discontinued by month 12. Blood counts were checked weekly for the first month, two weekly for the second month and monthly thereafter. A WBC count < $4000/mm^3$ was defined as leukopenia and < $1500/mm^3$ as severe leukopenia. 43 patients achieved remission in the CYC group. There were 5 severe infections in the CYC group including one death from CMV pneumonitis at 2.5 months (absolute lymphocyte count was $200/mm^3$). The paper mentions that total WBC, neutrophil and lymphocyte counts were lower in the CYC group from 1-15 months ($p < 0.01$), but does not mention absolute counts.

A prospective multicenter trial was conducted by Cohen et al.[38] in 2007 involving 48 patients with severe Churg-Strauss syndrome (CSS), with at least 1 poor-prognosis factor at baseline. These patients were treated with glucocorticoids and either 12 or 6 IV CYC pulses. All patients were treated with glucocorticoids and received 3 consecutive IV methylprednisolone (15 mg/kg) on days 1–3. Oral prednisone (1 mg/kg/day) was then taken for 3 weeks before being tapered by 5 mg every 10 days to 0.5 mg/kg/ day, then by 2.5 mg every 10 days to 15 mg/day, and finally by 1 mg every 10 days to the minimal effective dose or, when possible, until definitive

withdrawal. Monthly hematologic monitoring was required throughout CYC therapy. If the neutrophil count fell below 1,500/mm^3, the CYC dose was decreased 50%. 2 patients in the 6-pulse group died of CMV pneumonia and cardiac insufficiency at months 3 and 18, respectively. The 2 early deaths occurred during CYC therapy and both patients had neutropenia and lymphopenia; the patient that died of pneumonia was taking glucocorticoids (30 mg/day). There is no mention of absolute WBC counts in this manuscript.

In the MEPEX trial in 2007, Jayne et al.[39], investigated whether the addition of plasma exchange was more effective than IV methylprednisolone in the achievement of renal recovery in patients presenting with a serum creatinine > 5.8 mg/dl. 137 patients with a new diagnosis of ANCA-associated vasculitis confirmed by renal biopsy and serum creatinine > 5.8 mg/dl were randomly assigned to receive 7 plasma exchanges (n = 70) or 3 gm of IV methylprednisolone (n = 67). Both groups received oral CYC and oral prednisolone. Patient survival and severe adverse event rates at 1 yr were 51 (76%) of 67 and 32 of 67 (48%) in the IV methylprednisolone group and 51 (73%) of 70 and 35 of (50%) 70 in the plasma exchange group, respectively. A total of 244 adverse events were reported in 122 patients. Severe or life-threatening events occurred in 32 (48%) of 67 of the intravenous methylprednisolone group and 35 (50%) of 70 of the plasma exchange group. Leukopenia and infection were the most common adverse events. At least one episode of leukopenia occurred in 42/67 and 43/70 in the IV methylprednisolone and plasma exchange groups respectively. Infection was the leading cause of death (n=19).

Villa-Forte et al.[40] performed a retrospective review of patients in the GPA database

at the Center for Vasculitis Care at the Cleveland Clinic and included 82 eligible patients in the analysis. The initial treatment regimen for patients with severe disease was oral CYC 2 mg/kg/day with prednisone 1 mg/kg/day. From review of the charts, although this is a retrospective study, the paper mentions that the dose of CYC was adjusted to avoid a WBC count $\leq 4000/mm^3$. Patients were required to obtain a CBC every week for the first two months, then every 2 weeks for the next 2 months and monthly indefinitely thereafter. Upon achieving remission, the patients' immunosuppression regimen was switched from CYC to MTX. One patient died of polymicrobial sepsis in the study and 17% experienced serious infections (most commonly pneumonia). The decreased incidence of infections seen in this study compared to the NIH study was attributed to the fact that CYC was used for a shorter period of time in this study (3-6 months).

In a recent randomized trial[41] comparing oral and IV CYC for patients with ANCA-associated vasculitis, amongst 149 patients, 76 received IV and 73 received oral CYC therapy. In their protocol, the investigators checked blood counts on day 10 and 14 after each pulse and immediately before the next pulse in the IV CYC group. They reduced the dose of the subsequent pulse by 20% for patients with a leukocyte nadir of $2000 – 3000/mm^3$ and 40% for those with a nadir of $1000\text{-}2000/mm^3$. Eighty-seven leukopenic episodes occurred in 53 patients. Patients were less likely to be affected by leukopenia in the pulse group than in the daily oral group (20 [26%] patients vs. 33 [45%] patients; $P < 0.016$). Four patients in the pulse group experienced multiple episodes, compared with 15 in the daily oral group. The median time to the first leukopenic episode was 219 days (range, 14 to 549 days) in the pulse group and 68 days (range, 8 to 318 days) in the daily oral group (HR 0.41 [CI 0.23 to 0.71]). Only

10 of these episodes preceded or were associated with infection. 51 episodes of infection occurred in 41 patients. The median time to the first episode of infection was 147 days (range, 12 to 472 days) for the pulse group and 68 days (range, 9 to 533 days) for the daily oral group (HR, 0.88 [CI, 0.42 to 1.83]). Ten serious or life-threatening infections were observed in the daily oral group (one episode of pneumonia, one bowel perforation after diverticulitis, one *P. jirovecii* pneumonia with fatal outcome, and one herpes simplex infection and six episodes of infection not further characterized by the investigator) 3 of which were preceded by a leukopenic episode. Seven such episodes were observed in the pulse group (two with pneumonia, two with *Escherichia coli* sepsis, one with septic shock and one with perirectal abscess with subsequent perforation, and one infection not further characterized by the investigator). One episode of *E. coli* infection and the episode of septic shock were simultaneously associated with leukopenia.

Little et al.[21] recently reported an analysis of events responsible for mortality in patients with GPA and microscopic polyangiitis (MPA) from trials conducted by the EULAR (European League Against Rheumatism). An overall mortality of 56/524 (10.7%) in the first year was reported in the analysis. In 33 of the 56 patients who died (59%), the cause of death was classified as infection in 28 deaths (50%), whereas death as a result of active vasculitis occurred in only eight patients (14%). The investigators used a combined burden of events (CBOE) score that included infection, leukopenia and other adverse events. A score over 7 was associated with a probability of one-year mortality of 53% versus 5% for those with a score < 7. One hundred and forty-two episodes of infection occurred in 128/524 patients (24%); the commonest were bacterial respiratory tract infections (47 episodes) or generalized septicemia (29

episodes). Compared with no episode of leukopenia, leukocyte counts of 1000–2000/mm^3 and < 1000/mm^3 were associated with a hazard ratio for death within the first year of 2.6 (95% CI 1.1 - 6.3) and 6.7 (95% CI 2.9 - 15.5), respectively. At the time of leukopenia 74% of patients were on CYC. Half the infections occurred within the first 2 months.

The information above is tabulated below (Table 1) for easier review and comparison. The studies have been tabulated in a chronologic order from the earliest study first the most recent study last.

No.	Year	Investigators	Number of patients	Treatment regimen	Monitoring protocol	Comments
1	1973	Fauci et al.[8]	18	PO CYC 1-2 mg/kg/day. 3 patients with severe disease received IV CYC 2-4 mg/kg/d. Initial dose maintained for 10 days to 2 weeks. If no effect was observed, the dose was increased by 25 mg/d and again maintained for 10 days to 2 weeks. Dose escalation	Dose escalation continued till clinical response seen or WBC count < $3000/mm^3$	Clinical course of 12 patients tabulated in the paper. No serious infection or mortality from sepsis. No clear documentation of how many patients developed leukopenia in the cohort

				continued till clinical response seen or WBC count dropped < 3000/mm^3.		
2	1982	Cohen et al.[25]	75	18 patients with GPA treated with CYC and prednisone.	CYC was stopped if two successive neutrophil counts were < 2000/mm^3.	There were 70 infections in the patients with GPA. CYC was associated with infection only in the presence of neutropenia (preceded 13 infections in nine patients-12%).
3	1983	Fauci et al.[24]	85	Patients with GPA followed for 21 years. Treated with PO CYC 2	At induction, WBC count checked every other	One patient developed bacterial septicemia (the relationship to

				mg/kg/ with prednisone 1 mg/kg/d. The prednisone was subsequently changed to an alternate day schedule. For very severe disease, some patients treated with PO CYC 4-5 mg/kg/d with prednisone 2 mg/kg/d and subsequently switched to above regimen	day and once stabilized, every 1-2 weeks. Aim to keep WBC count > 3000 - 3500/mm^3.	leukopenia in this patient is not clearly mentioned)
4	1992	Hoffman et al.[26]	158	Induction regimen - CYC orally at 2 mg/kg with prednisone 1	Not mentioned	73 patients (46%) experienced 140 serious infections over

				mg/kg daily. After a month, prednisone tapered using an alternate day schedule to off over 6-9 months if the patient continued in remission. CYC continued for at least a year after remission, and then tapered by 25 mg every 2-3 months.		1229 patient years (0.11 infections per patient year) – pneumonia (57 episodes (39%), skin (38 episodes (26%), bacterial or fungal sepsis (13 episodes, (9%)). Overall mortality from infection was 3%.
5	1997	Adu et al.[27]	30	Compared IV CYC (n = 24) or PO CYC (n = 30) and prednisone in	Not mentioned	13/30 patients in the PO CYC group experienced leukopenia

				patients with primary systemic vasculitides in a randomized fashion.		(actual WBC count not available); number of infections during follow up was 1.66/patient (not statistically significantly different from IV CYC group). 2 patients in the IV CYC group died from septicemia.
6	1997	Guillevin et al.[28]	52	Randomized to receive prednisone plus IV CYC (group A) or prednisone plus PO CYC (group B) as first-line	Not mentioned	Infectious side effects were significantly more frequent in group B (69.6%) than in group A (40.7%) ($P<0.05$). The

				treatment. CYC given for at least 1 year and was then progressively tapered and discontinued.		incidence of *Pneumocystis carinii* pneumonia higher in PO CYC-treated patients (30.4%) than pulse CYC-treated patients (11.1%). Nine group A patients (33.3%) and 10 group B patients (43.5%) died.
7	1998	Haubitz et al.[29]	47	IV CYC (0.75 gm/m2) versus daily PO CYC treatment (2 mg/kg body weight in a prospective, randomized,	PO CYC dose increased if leukocyte counts >3,000/mm^3. Dose of CYC	60% patients receiving daily PO CYC, but only 18% of the patients receiving IV pulse CYC, developed at

				multicenter study in patients with ANCA-associated vasculitis and renal involvement. Cumulative CYC dose reduced by 57% in patients with IV CYC (n = 22) compared with patients treated with daily PO therapy (n = 25). For patients on PO CYC, CYC started at 1.5 mg/kg BW per	reduced in steps of 0.5 mg/kg BW. If leukocyte levels < 2,500/mm^3, dose reduced by 50%, and if the leukocyte counts <1,500/mm^3, drug was withheld until they increased above 2,500/mm^3. For IV CYC, CYC dose adjusted to	least 1 episode of leukopenia (leukocytes <3,000/mm^3) *(P* < 0.01). Severe lymphopenia (< 400) occurred in 86% patients with PO CYC administration and in 47% of patients with IV pulse CYC administration *(P* < 0.01). Severe infections occurred in 10 patients receiving daily PO CYC; 3 died of sepsis (one also had ongoing

				day and increased to 2 mg/kg BW per day after 2 weeks	the leukocyte count; aimed at a minimum of 3,000/mm^3. If the leukocyte nadir was < 2,500, the dose was reduced by 0.25 gm/m^2. In all but 4 patients, lymphocyte counts were monitored monthly.	disease activity). In the group receiving IV CYC, 3 patients developed severe infection and none died.
8	1999	Langford et al.[30]	31	Initially treated with oral CYC	CBC every 1-2 weeks	3 patients on CYC

				2 mg/kg/day with prednisone 1 mg/kg/day. Once in remission, patients were transitioned from CYC to MTX with prednisone being tapered to off guided by disease activity	with goal of maintaining WBC count > $3000/mm^3$ (neutrophil count > $1500/mm^3$).	experienced leukopenia requiring dose reduction; none had a neutrophil count of < $1500/mm^3$. 2 patients experienced serious infection (pneumonia), but no deaths.
9	2000	Reinhold-Keller et al.[31]	155	142 received CYC (137 oral and 5 pulse IV). Concomitant daily prednisone 1 mg/kg started in all patients with a generalized course; dosage	Not mentioned	56 serious infections requiring hospitalization, mostly pneumonia or sepsis observed in 41 patients (26%). In 5 patients, serious

				reduced to 5–10 mg/day within the first 3–6 months and then gradually tapered in steps of 1 mg/month.		infections (including 4 *S. aureus* septicemia and 1 pneumonia caused by an unidentifiable organism) in addition to active GPA led to death.
10	2003	Langford et al.[32]	42	PO CYC 2 mg/kg/day with prednisone 1 mg/kg/day. Once in remission, patients were transitioned from CYC to MTX with prednisone tapered to off	Not mentioned	Leukopenia requiring dose reduction of CYC occurred in 4 patients; one patient died from myocardial infarction in the study.

				guided by disease activity.		
11	2003	Jayne D et al.[33]	155	Patients with a new diagnosis of generalized vasculitis and a serum Cr ≤ 5.7 mg/dl. All patients received at least 3 months of therapy with PO CYC and prednisolone. After remission, patients were randomly assigned to continued CYC therapy (n = 73, 1.5 mg/kg body weight daily) or a substitute	CYC was discontinued if WBC count < 4000/mm^3. Study assessments (clinical and laboratory) were performed after 0, 1.5, 3, 6, 9, 12, 15, and 18 months and at the time of relapse, if it occurred.	55% patients (85/155) had at least one episode of neutropenia. Severe or life-threatening events occurred in 15 patients (10%) during the remission-induction phase, in 8 patients in the azathioprine group during the remission-maintenance phase (11%), and in 7 patients in the CYC group during the remission-

				regimen of azathioprine (n=71, 2 mg/kg/day).		maintenance phase (10%). Of 33 infections, 17 (52%) were associated with concurrent neutropenia. There were 8 deaths (5 %); 7 during the first 3 months.
12	2004	Langford et al.[34]	14	All patients were initially treated with oral CYC 2 mg/kg/day with prednisone 1 mg/kg/day. Once in remission, patients were transitioned from CYC to	CBC checked every 1-2 weeks with the goal of maintaining a WBC count > $3000/mm^3$ (neutrophil count > $1500/mm^3$).	2 patients required a dose reduction in CYC for leukopenia; none had a neutrophil count < $1500/mm^3$.

				MMF with prednisone being tapered to off guided by disease activity.		
13	2005	Harper et al.[35]	233	Retrospective, single centre, sequential cohort analysis of elderly patients (age > 65 years) with ANCA associated vasculitis. All patients received 2 mg/kg oral CYC until remission was achieved and prednisolone 60 mg/day	WBC counts checked at each clinic visit (the frequency of follow up is not mentioned in this retrospectiv e study). 25% dose reductions of CYC were made for those age > 65 yr	Risk of death increased in those who developed an infection requiring hospitalization (OR 1.58). Older patients more likely to develop infection (OR 1.9). Risk of infection in those who developed leukopenia was increased (OR 1.75).

				tapering to 7.5 mg/day by 6 months.	or leukopenia (WBC count < 4000/mm^3).	Leukopenia more likely to occur when patients were receiving CYC (OR 1.24). Severe renal disease (creatinine >400 μmol/l) also increased risk of leukopenia (OR 1.43).
14	2005	GPA Etanercept Trial[36]	180	RCT to evaluate etanercept for the maintenance of remission in patients with GPA. In addition to etanercept or	Not mentioned	49.4 % patients in each group had infections that ranged in severity from moderate to fatal. One patient in each group died from sepsis. No other

				placebo, patients received standard therapy (glucocorticoids plus CYC or MTX). Starting daily dose of prednisone 0.5 - 1.0 mg/kg body weight. At the investigators' discretion, patients with severe GPA could receive 1 gm of IVMP per day thrice before starting prednisone. Patients with limited disease		details available regarding WBC counts or infection.

				initially received 0.25 mg/kg MTX per week, and the dose was increased to a maximum of 25 mg per week. Patients with severe disease received CYC 2 mg/kg/d		
15	2005	DeGroot et al.[37]	100	Randomized patients without critical organ involvement from GPA to CYC 2 mg/kg/day PO (max150 mg/d) (n=49) or methotrexate 20-25 mg/week	CYC dosage reduced by 25 mg/d in patients aged > 60 years and withdrawn if WBC count < 4000/mm^3.	5 severe infections in the CYC group including one death from CMV pneumonitis at 2.5 months (absolute lymphocyte count 200/mm^3). Total WBC,

				(n=51). Once in remission, CYC reduced to 1.5 mg/kg/day until month 10 and then tapered and discontinued by month 12.	CBC checked weekly for the first month, two weekly for the second month and monthly thereafter. WBC count < 4000/mm^3 defined as leukopenia and < 1500/mm^3 as severe leukopenia.	neutrophil and lymphocyte counts lower in the CYC group from 1-15 months ($p < 0.01$); no mention of absolute counts)
16	2007	Cohen et al.[38]	48	Patients with severe Churg-Strauss syndrome, with	Monthly hematologic monitoring	2 patients in the 6-pulse group died of CMV pneumonia and

				at least 1 poor-prognosis factor at baseline. These patients were treated with glucocorticoids and either 12 or 6 IV CYC pulses. All patients treated with glucocorticoids and received 3 consecutive IVMP (15 mg/kg) on days 1–3. Oral prednisone (1 mg/kg/day) then taken for 3 weeks before being tapered	was required throughout CYC therapy. If the neutrophil count fell below 1,500/mm3, the CYC dose was decreased 50%.	cardiac insufficiency at months 3 and 18, respectively. The 2 early deaths occurred during CYC therapy and both patients had neutropenia and lymphopenia; the patient that died of pneumonia was on prednisone (30 mg/day). No mention of absolute cell counts available from this manuscript.

				by 5 mg every 10 days to 0.5 mg/kg/ day, then by 2.5 mg every 10 days to 15 mg/day, and finally by 1 mg every 10 days to the minimal effective dose or, when possible, until definitive withdrawal.		
17	2007	Jayne et al.[39]	137	Investigated whether addition of plasma exchange was more effective than IVMP in achieving renal	Not mentioned	Total of 244 adverse events were reported in 122 patients. Severe or life-threatening events occurred in 32/67 patients

				recovery in patients with a serum Cr > 5.8 mg/dl. Patients randomly assigned to receive 7 plasma exchanges (n = 70) or 3 gm of IVMP (n = 67). Both groups received PO CYC and PO prednisolone.		in the IVMP group and 35 (50%) of 70 of the plasma exchange group. Leukopenia and infection were the most common adverse events. At least one episode of leukopenia occurred in 42/67 and 43/70 in the IV methylprednisolone and plasma exchange groups respectively. Infection was the leading cause of death (n=19).
18	2007	Villa-Forte et	82	Retrospective	Paper	One patient died

		al.[40]		review of patients with GPA. Initial treatment regimen for patients with severe disease was oral CYC 2 mg/kg/day with prednisone 1 mg/kg/day. Upon achieving remission, the patients' immunosuppression regimen was switched from CYC to MTX.	mentions that the dose of CYC was adjusted to avoid a WBC count ≤ 4000/mm^3. Patients were required to obtain a CBC weekly for the first 2 months, then every 2 weeks for the next 2 months and monthly indefinitely	of polymicrobial sepsis in the study and 17% experienced serious infections (most commonly pneumonia). Decreased incidence of infections seen in this study compared to the NIH study attributed to shorter duration of CYC use (3-6 months).

					thereafter.	
19	2009	DeGroot et al.[41]	149	Randomized trial comparing PO and IV CYC for patients with ANCA associated vasculitis.	CBC on day 10 and 14 after each pulse and immediately before next pulse in IV CYC group. They reduced the dose of the subsequent pulse by 20% for patients with a leukocyte nadir of 2000 – 3000/mm^3 and 40%	87 leukopenic episodes in 53 patients. Patients less likely to be affected by leukopenia in the pulse group than in the daily PO group (20 patients vs. 33 patients; $P <$ 0.016). 4 patients in the pulse group experienced multiple episodes, compared with 15 in the daily PO group. Median time to first leukopenic

					for those with a nadir of 1000-2000/mm^3	episode 219 days in pulse group and 68 days in the daily PO group (HR 0.41). 10 of these episodes preceded or associated with infection. 51 episodes of infection in 41 patients. Median time to first episode of infection was 147 days for pulse group and 68 days for daily PO group (HR 0.88). 10 serious or life-threatening

						infections in the daily oral group; 3 of these preceded by leukopenia. 7 such episodes were observed in the pulse group.

CBC – complete blood count, CYC – cyclophosphamide, HR – hazard ratio, IV - intravenous, PO - per oral

Table 1. Summary of literature review regarding studies performing weekly and monthly CBC measurements in patients on oral CYC for severe GPA

Rationale for the proposed cost-effectiveness study

The above trial summaries suggest that CYC is an effective treatment for patients with severe manifestations of the small vessel vasculitides. It is therefore the standard of care in the management of these patients. However, it is clear that leukopenia and neutropenia are significant toxicities associated with the use of CYC. This complication has been reported in every study that has used CYC as part of the treatment regimen. GPA by itself does not predispose to infection through immunologic compromise though it may do so after the patient has sustained structural damage to the affected organs[18]. Increased non-specific IgG and IgA production has been reported in patients with GPA which may indicate B-cell lineage hyperactivity and probably indicating an absence of a compromised humoral component of the immune system.[6] Neutropenia has not been reported as a primary feature of GPA despite accelerated neutrophil turnover and reduced bone marrow functional reserve.[23]

Sepsis and potentially death are serious adverse outcomes and can very likely be prevented with appropriate monitoring. The need for strict and regular WBC count monitoring cannot be over emphasized. It is clear that there are no standardized recommendations for WBC monitoring while patients are on CYC therapy. The available data from published clinical trials that have used CYC as in the treatment reveal that the schedule for WBC monitoring is not part of the protocol (not mentioned in the published manuscript) or is very variable across studies. In studies that do mention the protocol for WBC monitoring, the frequency of monitoring varies from weekly to monthly. In addition to serious medical implications of suboptimal WBC count monitoring, there are associated serious potential cost implications of

missing the opportunity for intervention for leukopenia. These cost implications would extend from absence of development of infection to treatment of a non-life threatening infection with antibiotics to life-threatening sepsis requiring intensive care and potentially fatal outcome or significant morbidity. The other cost impact of the development of infection would be the need to temporarily discontinue or modify immunosuppressive therapy, which could lead to a severe flare up of the underlying disease, and the need for haematopoietic growth factors (such as granulocyte-colony stimulating factor) to try and replenish the neutrophil and leukocyte counts. Treatment with the haematopoietic growth factors could theoretically lead to a disease relapse as well. There are therefore multiple issues to consider regarding the consequences of leukopenia on the underlying disease and risk of infection. A cost-effectiveness analysis of the above mentioned monitoring strategy and its consequences has not been done before. This proposed cost effective analysis will therefore be an important step in establishing an evidence-based approach to WBC monitoring in patients on CYC.

Database of patients with GPA at the Cleveland Clinic

The database used for this analysis from the GPA database at the Cleveland Clinic created by Drs. Gary Hoffman and Alexandra Villa Forte. Since January 1992, all patients referred to the Cleveland Clinic with the diagnosis of GPA were considered for potential inclusion in the database. Patients were divided as having mild to moderate or severe disease based on disease features. Disease manifestations that were factored into assessing disease severity were musculoskeletal symptoms; cutaneous lesions, ear, nose and throat manifestations; ocular inflammatory features, focal pulmonary infiltrates or nodules, and glomerulonephritis. Severe disease was

defined as potentially organ-threatening or life-threatening such as diffuse alveolar hemorrhage, rapidly progressive renal failure with a serum creatinine of >2 mg/dl, peripheral or central nervous system disease, gastrointestinal ischemia, and sight-threatening ocular disease (retinal ischemia, scleritis, orbital pseudotumor). The database carefully excluded patients who had established disease and who were being treated by referring physicians before their referral. In addition, patients with new-onset disease were excluded if they were referred only for a single visit or only followed up on an annual basis. Patients with severe disease were treated with a regimen for remission induction of daily oral CYC (2 mg/kg, adjusted for renal function and white WBC count) and glucocorticoids (GCS), usually as prednisone 1 mg/kg daily. For patients with mild to moderate disease, initial treatment was with weekly low-dose MTX (15 mg/wk, increased over 4–8 wk to 25 mg/wk, if tolerated and necessary for remission) and GCS (1 mg/kg daily). All patients met the American College of Rheumatology (ACR) criteria for the classification of GPA. Records of all patients meeting inclusion criteria were included from January 1992 to December 2004.

METHODS

Descriptive Analysis of the CCF GPA Database

The analysis of the data for descriptive purposes was done using the statistical software R (version 2.11.1). The database was available as a set of comma separated version (csv.) files each corresponding to a particular case report forms that had been used for documentation of disease characteristics and disease activity (for example, the csv. file named "treat" contained the details of all treatments administered to the patients). A sub-dataset of patients was created who had received CYC, using the unique drug code for cyclophosphamide. Unique patients who had received CYC were identified by using their patient ID numbers. For purposes of this analysis, leukopenia was defined as WBC count < 4000/mm^3, a definition that has been used in previous studies[17, 19]. This definition was used to analyze the database laboratory measurements to generate a list of unique ID numbers. Severe leukopenia was defined as WBC < 2000/mm^3. Paper charts were then reviewed to evaluate the following issues:

1. Whether the patient developed leukopenia while on CYC.
2. Consequences of leukopenia – recovery of WBC count, infection, need for hospitalization.
3. Severity of infection
4. Outcome of severe infection

Definition of the Cost Effectiveness Analysis (CEA) Model

Reference case:

Forty five year old patient with severe GPA on daily oral CYC for three months

Strategies:

(a) Weekly CBC monitoring

(b) Monthly CBC monitoring

Time Horizon:

Three-month period during which patients are expected to be on CYC as induction therapy for new diagnosis or severe relapse of GPA

Perspective:

Analysis was performed from a societal perspective. There has been a tremendous increase in healthcare expenditures in the United States.[42] The rate of increase in U.S. health care spending decreased in 2009 to 4% compared to 4.7% in 2008. Total health expenditures reached $2.5 trillion, translating to $8,086 per person or 17.6 % of the Gross Domestic Product (GDP). The rate of spending on clinical services decreased to 4% in 2009 from 5.2% in 2008. These decreases in 2009 were partially offset by increasing prices. Hospital spending increased 5.1% in 2009 compared to 5.2% growth in 2008. Over 2009 – 2019, it is projected that the average annual health spending growth (6.1%) will increase beyond the average annual growth rate of the overall economy (4.4%). By 2019, national health spending is expected to reach $4.5 trillion and comprise 19.3 percent of GDP. As a result of more rapid growth in public spending, the public share of total health care spending is expected to reach 52% by 2019[42].

This CEA was performed from a societal perspective. The frequency of CBC monitoring in patients with GPA on CYC can potentially detect severe leukopenia

allowing for earlier intervention by the treating physician (changing the dose of CYC, temporary or permanent discontinuation of CYC, continuation at same dose with continued weekly WBC monitoring) with the potential to prevent severe leukopenia, severe infection and mortality. The costs incorporated into the analysis for comparing the two monitoring strategies included the costs of CBC measurement, evaluation by physician in the outpatient office regarding leukopenia or infection, evaluation in the emergency department for severe infection, outpatient antibiotics for infections (respiratory, urinary tract and skin) and admission to the hospital for severe infection/sepsis. Since the time period for analysis was three months, no discounting was performed.

Effectiveness Measure:

Quality Adjusted Life Years (QALY).

Literature review

The literature (PubMed) was searched using search terms "cyclophosphamide", "Wegener's granulomatosis", and "trial". The initial search returned a combination of case reports, small case series, observational studies, retrospective analyses and randomized controlled trials. Studies were strictly selected for inclusion if they included patients with GPA who had received oral CYC or both oral and intravenous CYC. When there were studies that included patients on both oral and intravenous CYC, only data regarding the oral CYC group was extracted into the tables as shown below. The selected studies were carefully screened for the following data: strategy for monitoring complete blood count, incidence of leukopenia (severe and non-severe), incidence of infectious complications (severe and non-severe) and mortality

attributable to infection. Separate tables were constructed to list the details of the studies included and for the required probabilities for the CEA decision tree and sensitivity analyses. The literature was also reviewed for studies of sepsis to determine costs and quality of life in patients with GPA, and in patients with survival after sepsis.

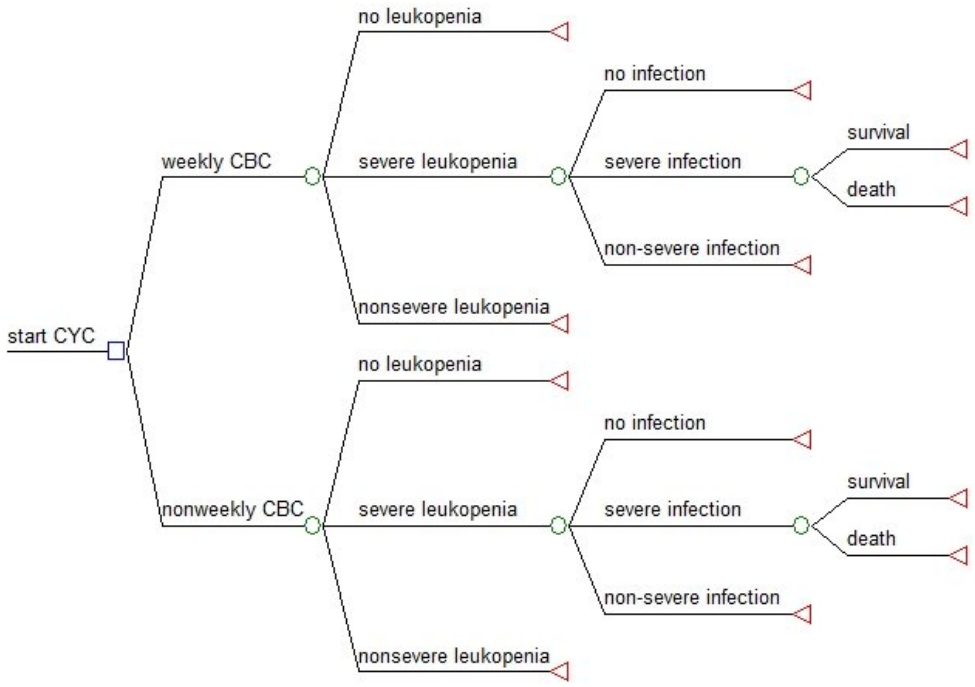

Fig 1. Decision analysis tree for cost effectiveness analysis

The cost effectiveness analysis was performed using TreeAge Pro™ 2009 software by constructing a decision analysis tree to compare the two strategies: weekly versus monthly CBC monitoring. The probabilities for each event were entered based on the Cleveland Clinic GPA database and published literature for the weekly CBC arm and solely from published literature for the monthly CBC arm. The analysis included the probability of leukopenia (absent, severe, non-severe), infection (absent, severe and non-severe), and survival and death as a consequence of severe infection. Health-

related quality of life measures were assigned to each event. Direct medical costs were examined from a societal perspective (i.e., all direct costs and benefits regardless of whether they are incurred by the patient, employer, provider, or a third party payer). One-way sensitivity analyses were performed to test the robustness of the findings over a range of probabilities for all variables (expected values and payoffs) entered into the decision tree and probabilistic sensitivity analysis was performed to estimate the effects of parameter uncertainty on the obtained results.

Probabilities for CEA

The probabilities that were entered into the decision tree were calculated as means of the raw probabilities obtained from the Cleveland Clinic database and published literature (Table 9). A range of probabilities were used to enter the ranges for the one-way sensitivity analyses on the decision tree based on literature review (Table 9). If a range of probabilities for a certain variable were not available, the mean values were entered by consensus and a wide range (0.01 – 0.99) was selected for the one-way sensitivity analyses for that particular variable. For the purposes of our analysis, patients who did not experience infectious complications and those who had non-severe infections were assigned the same QALY estimate as the presence of non-severe infections was assumed to have little additional long-term impact on the quality of life beyond that involving stable disease activity on immunosuppression. Formulae were used to generate complementary probabilities at the chance nodes as the probabilities of all branches emanating from a chance node have to add up to 1.0. These formulae allowed the software to automatically adjust probabilities for two branches of the chance node as the probability of the third branch was being varied over the desired range.

Weekly CBC arm

Study	N Oral CYC	Severe leukopenia N (%)	Non-severe leukopenia N (%)	Severe Infection given severe leukopenia N (%)	Non-severe infection given severe leukopenia N (%)	Deaths from infection N (%)
Fauci	18	0 (0)	Not known	0 (0)	Not known	0 (0)
Fauci	85	0 (0)	Not known	1 (0.01)	Not known	0 (0)
Langford	42	0 (0)	4 (0.10)	2 (0.05)	Not known	0 (0)
Langford	14	0 (0)	2 (0.14)	3 (0.21)	Not known	0 (0)
CCF GPA database	98	8 (0.08)	37 (0.40)	3 (0.03)	Not known	1 (0.01)

Monthly CBC arm

Study	N	Severe leukopenia N (%)	Non-severe leukopenia N (%)	Severe Infection given severe leukopenia N (%)	Non-severe infection given severe leukopenia N (%)	Deaths from infection N (%)
Haubitz	25	15 (0.6)	Not known	6 (0.24)	Not known	3 (0.12)
Jayne	155	7 (0.045)	30 (0.19)	4 (0.03)	3 (0.019)	5 (0.03)
Jayne	137	15 (0.11)	70 (0.51)	8 (0.06)	24 (0.17)	19 (0.14)
DeGroot	73	11 (0.15)	26 (0.36)	5 (0.07)	11 (0.15)	5 (0.07)

Table 2. Studies included in calculation of probabilities of clinical events for decision analysis.

Variable	Strategy	Value (%)	Range (%)	Reference No.
No leukopenia	Weekly	0.78	0.01 – 0.99	Consensus
	Monthly	0.44	0.01 – 0.99	Consensus
Non-severe leukopenia	Weekly	0.20	0.01 – 0.40	8,24,32,34, CCF GPA database
	Monthly	0.33	0.19 – 0.51	33,37,39
Severe leukopenia	Weekly	0.02	0.01 – 0.08	8,24,32,34, CCF GPA database
	Monthly	0.23	0.01 – 0.60	33,37,39,41

No infection given severe leukopenia	Weekly	0.86	0.44 - 0.89	Consensus
	Monthly	0.79	0.50 - 0.98	Consensus
Non-severe infection given severe leukopenia	Weekly	0.11	0.10 – 0.30	Consensus
	Monthly	0.11	0.10 – 0.40	33,37,39,41
Severe infection given severe leukopenia	Weekly	0.02	0.01 – 0.46	8,24,32,34, CCF GPA database
	Monthly	0.10	0.02 – 0.29	29,33,37,39,41
Survival after experiencing sepsis as a result of severe leukopenia	Weekly	0.99	0.01 – 0.99	8,24,32,34, CCF GPA database
	Monthly	0.94	0.86 – 0.98	29,33,37,39,41

Table 3. Mean values and ranges for parameters used for 1-way sensitivity analyses

Costs involved in CEA

Costs for CBC, rheumatology office evaluation and management of sepsis were obtained from Centers for Medicare and Medicaid Services. Cost of emergency room visit was obtained from the Medical Expenditure Payment Survey performed by the Agency for Healthcare Research and Quality, US Department of Health and Human Services[29]. Costs of generic medications were obtained from the pharmacy retail cost database at the Cleveland Clinic. All costs were estimated for a three-month course of CYC therapy, which is the usual duration of its use as induction therapy for GPA. For medication costs, we used the average wholesale price incurred by the hospital pharmacy. At $1.75 per 50 mg CYC tablet, the three-month cost of a daily regimen was estimated to be $472.00. For the weekly arm, the cost of CBC at $65 per measurement was calculated for 12 CBC measurements ($ 780), whereas for the monthly arm, the costs entered were for 3 CBC measurements ($ 195). The cost of antibiotics likely to be used on an outpatient basis for non-severe infections were

calculated based on the cost of a single pill and likely duration of therapy. Costs associated with weekly and monthly CBC measurements, no leukopenia, non-severe leukopenia, no infection, non-severe infection, and survival following sepsis was calculated using the abovementioned costs. All costs were adjusted to 2010 US dollars.

Antibiotic (mg)	**Cost of single pill ($)**	**Duration of therapy (days)**	**Cost ($)**
Amoxicillin (500)	0.14	10	8.40
Amoxicillin-clavulanic acid (Augmentin) (875)	1.02	10	20.40
Levofloxacin (500)	17.14	7	119.98
Nitrofurantoin (100)	2.80	10	56.00
Ciprofloxacin (500)	0.06	10	1.20

Table 4. Costs of outpatient antibiotic therapy

Cost parameter	**Estimate ($)**	**Range ($)**	**Source**
CBC measurement	65	10 - 100	CMS[42]
Three months of oral CYC therapy	472	250 - 650	CCF Retail pharmacy
Outpatient rheumatology clinic visit (level 5)	150	50 - 250	CMS[42]

Emergency room evaluation	1200	500 - 1500	MEPS, AHRQ[43]
Cost of outpatient antibiotic therapy	60	20 - 120	CCF Retail pharmacy
Sepsis management	47000	20000 - 100000	CMS[42]

AHRQ – Agency for Healthcare Research and Quality, CMS – Center for Medicare and Medicaid Services, MEPS – Medical Expenditure Panel Survey

Table 5. Cost ranges for sensitivity analysis

Estimation of quality of life and QALY parameters

The following assumptions and calculations were used to generate the QALY parameters for the cost effectiveness analysis. The average life expectancy in the US based on US Social Security Administration Actuarial Life Tables[44] is 80 years. Matteson et al.[45] reported long term follow up on a cohort of patients with GPA in 1996 and noted that there is a rapid decrease in survival among patients with GPA within the first year of follow-up that persists over the course of the disease. At 5 years of follow-up, the observed survival was 75% of that of the general population. Adjusting for 15 years of progress in the management of patients with GPA including changes in trends of therapy and management, a 10% reduction in life expectancy was applied to the current patient cohorts resulting in an average life expectancy of patients with GPA of 72 years. The age of patients with adult onset GPA is 40 - 60 years; a mean age parameter of 45 years was used, which resulted in a life expectancy since diagnosis of GPA of 27 years. Patients with GPA as well as those with sepsis experience significant compromise of quality of life. In a study by Hoffman et al.[46] in

1998, patients with median 5 year duration of GPA reported that their income was reduced by a median of 26% at 1 year after disease onset. The authors extrapolated that at least $9.7 million per year is lost in income to patients with GPA[46]. Quality of life measures (QALY) in patients with uncomplicated GPA (without severe leukopenia or severe infection), in those experiencing non-severe infections and in those surviving after sepsis were factored into the analysis. Based on this study, the quality of life (QoL) at baseline with severe GPA on oral CYC[45] was calculated as decreased by 30% resulting in a QALY at baseline with severe GPA on oral CYC of 18.9 QALY. The development of severe infection/sepsis is expected to further compromise the quality of life of a patient with GPA on CYC as it does in other illnesses[47]. The adjustment for QALY measures for sepsis was based on review of the sepsis literature. The baseline QoL was further decreased by 20% to calculate the average QALY associated with sepsis in patients on weekly CBC monitoring. To factor in the possibility of increased severity of infection in the monthly CBC arm owing to the increased severity of leukopenia, the baseline QoL was discounted by 40%. However, they were subjected to the same ranges for sensitivity analyses. The other discounts that were applied to this baseline QoL (such as that associated with non-severe leukopenia and non-severe infection) are based on consensus, as these estimates are not available in the literature.

The calculation of QALY parameters was generated as a product of the baseline quality of life (0.7 for patient with GPA), an adjustor for a clinical situation (presence or absence of leukopenia or infection) and the life expectancy. For example, the QALY calculation for a patient on weekly CBC with no leukopenia would involve the product of the baseline QoL, the adjustor for no leukopenia and the life expectancy.

The absence of leukopenia or infection in either arm is not expected to have any impact on the baseline quality of life (parameter value = 1.0).

The median age in the CCF GPA database is 47 years and the analyses were performed for a base case age of 45 years. However, patients with GPA in the published literature tend to be older (55-65 years), so age was also introduced as a variable for sensitivity analyses. Since the QALY calculation involves age after diagnosis, the base parameter for life expectancy with diagnosis was maintained as 27 years (considering an age 72 years and diagnosis with GPA at age 45 years) and range of 7-37 years was used (accounting for actual patient age of 35 years to 65 years).

QALY variable	**Base estimate (QALY)**	**Range of utilities for sensitivity analysis**	**Reference No.**
Baseline	0.7	0.6 – 0.9	44, 45, 46
Weekly CBC arm - adjustors			
No leukopenia	1.0	0.99 – 1.0	44, 45, 46
Non-severe leukopenia	0.96	0.94 – 0.99	44, 45, 46
No infection	1.0	0.99 – 1.0	44, 45, 46
Non-severe infection	0.96	0.94 – 0.99	Consensus
Sepsis	0.8	0.7 – 0.9	47
Monthly CBC arm - adjustors			
No leukopenia	1.0	0.99 – 1.0	44, 45, 46
Non-severe leukopenia	0.96	0.94 – 0.99	44, 45, 46

No infection	1.0	0.99 – 1.0	44, 45, 46
Non-severe infection	0.96	0.94 – 0.99	Consensus
Sepsis	0.8	0.7 – 0.9	Consensus

Table 6. QALY estimates and ranges for sensitivity analysis

After entering the probabilities, costs and estimates of QALYs in the decision tree, an initial roll back analysis was performed. A cost effectiveness analysis was performed next and followed by a one-way deterministic sensitivity analysis performed for each variable in the decision tree. Finally, a probabilistic sensitivity analysis (Monte Carlo simulation) was also performed for 2^{nd} order uncertainty using the Dirichlet distribution set up to do repeated sampling and analyses from 1000 samples. Probabilistic sensitivity analysis provides similar insights to deterministic sensitivity analysis, and can also quantify the level of confidence that can be placed in the model's results. The Dirichlet distribution is a multivariate distribution whose components all takes values on (0, 1) and which sum to one. This distribution can be used to represent the uncertainty in all of the probabilities of a chance event. During Monte Carlo simulation, the distribution can sample probabilities for each branch, while ensuring that probabilities sum to 1.0.

RESULTS

Demographic data

Demographic data was available on 130 patients. There were 62 females (47%) and 69 males (53%). Of the 130 patients, 123 (94%) were Caucasian, 2 (2%) were Asian, 2 (2%) were Hispanic, 3 (2%) other (including mixed race) and 1 (1%) unknown. The median age was 47 years (Interquartile Range 34 – 56 years). 26 (20%) patients were diagnosed with GPA at the Cleveland Clinic and 104 (80%) were diagnosed prior to referral. 129 (98%) were alive at follow up over the duration of the study. 72 patients (57%) has never smoked, 39 patients (31%) had a past history of smoking, 12 patients (9%) were current smokers and smoking status was unknown in 3 patients (2%).

Clinical manifestations

The clinical manifestations of patients at presentation and over the course of the study are shown in Table 7.

Organ system	Clinical manifestation	At presentation N (%)	Over course of the study N (%)
Upper respiratory tract	Nose (other than saddle nose)	61 (46.9)	108 (83.0)
	Saddle nose	4 (3.1)	24 (18.4)
	Sinus	69 (53.1)	111 (85.3)
	Oral mucosa or tongue lesion	5 (3.8)	23 (17.6)

Ear	Ear pain	18 (13.8)	50 (38.5)
	Otitis media	24 (18.4)	46 (35.4)
	Conductive hearing loss	27 (20.7)	58 (44.6)
	Sensorineural hearing loss	2 (1.5)	9 (7)
	Mastoiditis	4 (3.1)	7 (5.4)
	Tinnitus	4 (3.1)	13 (10)
Eye	Conjunctivitis	2 (1.5)	17 (13.1)
	Episcleritis	0 (0)	7 (5.4)
	Scleritis	0 (0)	5 (3.8)
	Iritis	0 (0)	2 (1.5)
	Proptosis or retro-orbital pseudotumor	2 (1.5)	11 (8.5)
	Corneal involvement	0 (0)	1 (0.8)
	Retinal disease	0 (0)	1 (0.8)
	Blindness	1 (0.8)	4 (3.1)
	Lacrimal duct involvement	0 (0)	10 (7.7)
Skin	Palpable purpura	2 (1.5)	15 (11.5)
	Subcutaneous nodules	2 (1.5)	11 (8.5)
	Livedo	0 (0)	3 (2.3)
	Skin infarction	0 (0)	11 (8.5)

	Skin ulcer	2 (1.5)	13 (10)
	Raynaud's phenomenon	1 (0.8)	2 (1.5)
Systemic symptoms	Fever (> 100 deg F)	23 (17.7)	60 (46.1)
	Weight loss (> 5%)	11 (8.5)	36 (27.7)
Pulmonary and lower respiratory tract	Cough	24 (18.5)	74 (56.9)
	Dyspnea	17 (13.1)	70 (53.8)
	Hemoptysis	11 (8.5)	45 (34.6)
	Infiltrates	15 (11.5)	67 (51.5)
	Nodules	11 (8.5)	55 (42.3)
	Pleuritis	3 (2.3)	15 (11.5)
	Fibrosis	0 (0)	3 (2.3)
	Subglottic stenosis	2 (1.5)	18 (13.8)
Gastrointestinal	Ischemia	0 (0)	0 (0)
	Gallbladder involvement	0(0)	0 (0)
Kidney	Overall renal involvement	11 (8.5)	68 (52.3)
Nervous system	Peripheral nervous system - sensory	1 (0.8)	17 (13.1)
	Peripheral nervous system – motor	3 (2.3)	6 (4.6)
	Mononeuritis	1 (0.8)	4 (3.1)
	CNS lesion	0 (0)	0 (0)

	Meningitis	0 (0)	1 (0.7)
	Cranial nerve involvement	0 (0)	5 (3.8)
	Diabetes insipidus	0 (0)	1 (0.7)
Musculoskeletal	Joint involvement	30 (23.1)	93 (71.5)
Breast disease	Biopsy proven disease	2 (1.5)	4 (3.1)
Parotid gland	Biopsy proven disease	0 (0)	1 (0.7)
Heart	Vasculitis - biopsy proven	0 (0)	0 (0)
	Vasculitis – non biopsy proven (coronary event)	0 (0)	1 (0.7)
	Myocarditis – biopsy proven	0 (0)	0 (0)
	Myocarditis – non biopsy proven	0 (0)	0 (0)
	Sudden death	0 (0)	0 (0)
	Arrhythmias	0 (0)	0 (0)
	Pericarditis	0 (0)	2 (1.5)
Prostate	Biopsy proven	0 (0)	1 (0.7)
Bladder	Biopsy proven	0 (0)	1 (0.7)
Female genital	Cervical/vaginal	2 (1.5)	2 (1.5)

tract	disease		
Other	Other organ system	14 (10.8)	43 (33.1)

Table 7. Clinical manifestation in patients with Wegener's granulomatosis in the database at enrolment and over the course of the study

Baseline labs

The baseline labs indicate the time of the first visit to the Cleveland Clinic.

Laboratory statistic (variable)		**Median (Interquartile range)**
WBC count (X 1000 cells/mm^3)		9.33 (6.80 – 11.55)
Hemoglobin (grams/dl)		13.00 (11.4 – 14.00)
Platelets (X 1000 cells/mm^3)		299 (224 – 355)
ESR (mm/h)		34 (13 – 67)
CRP (mg/dl)		1.3 (0.6 – 4.9)
Serum creatinine (mg/dl)		1.00 (0.8 – 1.3)
Hematuria	Yes	35 (28%)
	No	90 (71%)
	Unknown	2 (2%)
RBC casts	Yes	3 (2%)
	No	116 (91%)
	Unknown	8 (6%)
AST levels (U/L)		18 (15 – 22)
Alkaline phosphatase (U/L)		80 (66 – 106)
IgG levels		1240 (627 – 1290)

Table 8. Baseline laboratory characteristics

Anti-neutrophil cytoplasmic antibody (ANCA) testing

The result of ANCA testing showed a c-ANCA pattern in 76 (81%) and p-ANCA pattern in 15 (16%) patients by indirect immunofluorescence. The ELISA was positive for anti-proteinase 3 (PR3) antibody in 28/37 (76%), anti-myeloperoxidase (MPO) antibody in 8/40 (22%) patients.

Chest radiographic (CXR) findings

CXR information was available on 787 CXR performed in 130 patients. Infiltrate on CXR was noted in 182 (23%) of CXR, not observed in 585 (74%) and status unknown in 20 (3%). Compared with previous CXR, 32 (17%) showed improvement, 55(29%) showed worsening and unchanged in 25 (13%). The pattern was focal in 77 (46%), diffuse in 61 (37%), ands status unknown in 27 (16%). Nodule was noted in 235 (30%), absent in 540 (69%) and status unknown in 12 (2%). In 52 (22%) cases, the nodule was improved; in 64 (27%) it was felt to have worsened and was unchanged in 44 (18%) cases. The nodules were single in 57 (25%) and multiple in 159 (70%). Diffuse pulmonary fibrosis was noted in 21 (3%) and absent in 722 (92%). Comparing with previous CXR, it was improved in 1 (5%), worsened in 12 (55%).

Biopsy data

Vasculitis noted on biopsies in 60 (28%) patients, not seen in 124 (57%) patients and unknown in 32 (15%) patients. Granulomas were absent in biopsies from119 (55%) patients, present in 65 (30%) patients and unknown in 32 (15%) patients. Necrosis was reported in biopsies from 20 (10%) patients, not seen in 179 (86%) patients, and

unknown in 9 (4%) patients. In renal biopsies, glomerulonephritis was present in 20 (10%) patients, absent in 180 (87%) patients, and unknown in 9 (4%) patients. Crescents were present in 21 (10%) patients, absent in 180 (87%) and unknown in 7 (3%) patients.

Biopsy site	Vasculitis absent	Vasculitis present	Unknown
Nose	25	11	4
Sinus	24	5	2
Lung	37	20	12
Kidney	17	3	5
Peripheral nerve	0	1	0
Muscle	0	1	0
Skin	3	9	1
Trachea	9	1	3
Heart	0	1	0
Gastrointestinal	1	0	0
Prostate	0	1	0
Breast	0	1	2
Bladder	0	0	1
Cervical/vaginal	0	3	0
Gingival	2	0	1
Orbit	1	2	1
Mastoid	3	0	0
Ear	1	0	0

Table 9. Incidence of vasculitis in biopsy specimens of patients with GPA

Drug therapy

Ninety-eight patients had received repeated treatment with CYC (total 441 treatments), suggesting that most patients had received CYC multiple times as induction therapy for GPA or for severe relapsing disease.

Name of medication	Number of patients
Prednisone	127
Cyclophosphamide	98
Azathioprine	45
Methotrexate	95
Mycophenolate mofetil	1
Trimethoprim-sulfamethoxazole	60
Methylprednisolone	30
Infliximab	14
Etanercept	14
Chlorambucil	2
Tacrolimus	10
Cyclosporine	4
Intravenous immunoglobulin	1

Table 10. Medications used for treatment of patients with GPA in the database

Drug toxicities

Drug toxicities were experienced by 70 patients. 17 (24%) patients on prednisone, 27 (39%) patients on CYC, 10 (14%) patients on azathioprine and methotrexate each, 2

(3%) patients on chlorambucil and trimethoprim/sulfamethoxazole each, and 1 (1%) of patients on tacrolimus and methylprednisolone each.

Clinical disease activity status over the course of the study

Clinical disease activity was assessed using the Birmingham Vasculitis Activity Score-WG (BVAS/WG), with a score of 0 indicating remission. These data are derived on serial assessments of patients and therefore there is overlap in the numbers of patients in the comments column, i.e. a patient who had active disease would have remission of his disease followed by a flare (minor or major as indicated by the physician assessment and BVAS/WG scores).

Variable	No. of patients	Comments
Patient condition (physician's impression in the chart)	130	All 130 patients had active disease initially; 124 experienced remission at some time, 40 had a smoldering course and 88 experienced a relapse of their disease
Disease status judged by BVAS	130	123 patients were deemed to be in remission, 84 had persistent limited disease, 25 had persistent severe disease, 121 had a limited flare of disease and 77 had a severe flare of disease
Total BVAS score (number of patients)		0 (120), 1 (91), 2 (81), 3 (85), 4 (56), 5 (41), 6 (37), 7 (33), 8 (15), 9 (15), 10 (8), 11 (6), 12 (5), 13 (1), 14 (2), 21 (1)

Table 11. Disease activity and clinical status of patients over period of the study

Leukopenia and infectious complications

Fifty-four patients experienced 128 episodes of leukopenia. Of 98 patients that received CYC, 47 patients had developed leukopenia at some point along the course of the study. 27 of these patients had experienced 53 infections during the course of their follow up. The 53 infection sites were lung in 21 patients (40%), skin in 13 patients (25%), eyes in 1 patient (2%), bloodstream in 9 patients (17%), esophagus in 1 patient (2%), unknown in 4 patients (8%), urinary tract in 3 patients (6%) and other in 1 patient (2%). 11 patients in the CYC group developed infectious complications. Upon review of the paper charts, data from 45 patients was available for analysis regarding leukopenia and infectious complications. Eight of these patients developed severe leukopenia, 37 had non-severe leukopenia. Upon comparison of the leukopenia, infection and CYC databases, five patients with severe leukopenia had and 22 patients with non-severe leukopenia had experienced severe infections. Information regarding non-severe infections was not collected as the creators of the database felt that those would be too numerous and of little consequence (e.g. minor infections such as upper respiratory tract infections or uncomplicated bronchitis).

Decisions regarding CYC when leukopenia was detected

Data regarding decisions made in patients on CYC when leukopenia (WBC count < 4000/mm^3) was detected was available on 26/47 patients (Table 12).

Decision regarding CYC	Number of patients
Continued at same dose	4

Dose reduced and continued at the reduced dose	10
Discontinued	6
Temporarily held and then restarted at original dose	6
Medication switched from CYC to another immunosuppressant	8

Table 12. Decisions regarding CYC upon detection of leukopenia

Results of Cost Effectiveness analysis

In the base case analysis, in a 45-year-old patient with severe GPA on CYC for three months, the expected cost and effectiveness of using weekly CBC monitoring is $1572 and 18.90 QALYs and that of monthly CBC is $2151 and 18.14 QALYs respectively. The gain in effectiveness is 0.76 QALY. The weekly CBC strategy dominates (is less expensive and more effective than) the monthly CBC strategy in this analysis. The effectiveness of CBC monitoring in patients with GPA on daily oral CYC was most heavily influenced by the frequency of leukopenia (absent, severe and non-severe) in the monthly CBC arm. Please refer to Tables 14, 15 and 16 below for influence of other variables. The cost of CBC monitoring in patients with GPA on daily oral CYC was most heavily influenced by the frequency of severe leukopenia in patients in the weekly CBC arm of the study. The sensitivity analysis for age (Table 17) indicates that the results would be applicable to younger and older patients than the base case analysis.

The 1-way sensitivity analysis revealed dominance of the weekly CBC strategy over the monthly CBC strategy (weekly strategy was more effective and less expensive) for all variables except the following scenarios.

Current strategy	**Event**	**Threshold**	**Cost-effectiveness outcome**
Weekly	Non-severe leukopenia	≥ 30%	Monthly CBC more expensive but equally effective
Weekly	Cost of sepsis	≤ 27000	Weekly CBC more expensive and effective
Weekly	No leukopenia and lower quality of life	≤ 0.99	Monthly CBC more expensive and effective
Monthly	Severe leukopenia	≤ 16%	Weekly CBC more expensive and effective
Monthly	Non-severe leukopenia	≥ 48%	Weekly CBC more expensive and effective
Monthly	No infections	≥ 90%	Weekly CBC more expensive and effective
Monthly	Severe infections	≤ 7.5%	Weekly CBC more expensive and effective
Monthly	Non-severe	≥ 26%	Weekly CBC more expensive and

	infection		effective

Table 13. Scenarios based on probability sensitivity analysis where the weekly CBC strategy does not dominate the monthly CBC strategy

The variables that were most robust to the 1-way sensitivity analyses were the probability of survival in patients with severe infection given severe leukopenia in both groups of patients (weekly and monthly CBC monitoring) and costs associated with outpatient antibiotic therapy, costs associated with emergency room visit, cost of monthly CBC monitoring and all the quality of life measures.

Variable	Parameter Range	Cost per patient, weekly CBC monitoring ($)	Effective-ness per patient, weekly monitoring (QALY)	Cost per patient, monthly CBC monitoring ($)	Effectiveness per patient, monthly monitoring (QALY)	Marginal cost/ QALY ($)
Baseline		1581	18.74	2070	18.52	Dominated (monthly)*
No leukopenia in weekly monitoring arm						
	0.01	1792	18	2070	18	Dominated (monthly)
	0.99	1565	19	2070	18	Dominated (monthly)
Severe leukopenia in weekly monitoring arm						
	0.01	1562	19	2070	18	Dominated (monthly)
	0.08	2171	18	2070	18	Dominated (monthly)
Non-severe leukopenia in weekly monitoring arm						
	0.10	1653	19	2070	18	Dominated (monthly)
	0.40	1587	18	2070	18	674
No infection given severe leukopenia in weekly monitoring arm						
	0.01	1923	19	2070	18	Dominated (monthly)
	0.9	1563	19	2070	18	Dominated

						(monthly)
Severe infection given severe leukopenia in weekly monitoring arm						
	0.01	1561	19	2070	18	Dominated (monthly)
	0.46	2040	19	2070	18	Dominated (monthly)
Non-severe infection given severe leukopenia in weekly monitoring arm						
	0.01	1878	19	2070	18	Dominated (monthly)
	0.30	1567	19	2070	18	Dominated (monthly)
Survival in patients with severe infection given severe leukopenia in weekly monitoring arm						
	0.01	1580	19	2070	18	Dominated (monthly)
	0.99	1581	19	2070	18	Dominated (monthly)
No leukopenia in monthly monitoring arm						
	0.01	1581	19	3550	18	Dominated (monthly)

	0.99	1581	19	998	19	Dominated (weekly)
Severe leukopenia in monthly monitoring arm						
	0.01	1581	19	989	18	3193
	0.60	1581	19	4587	18	Dominated (monthly)
Non-severe leukopenia in monthly monitoring arm						
	0.19	1581	19	2588	18	Dominated (monthly)
	0.51	1581	19	1048	18	515
No infection given severe leukopenia in monthly monitoring arm						
	0.50	1581	19	3378	18	Dominated (monthly)
	0.98	1581	19	1139	18	2079
Severe infection given severe leukopenia in monthly monitoring arm						
	0.02	1581	19	1140	18	1921
	0.24	1581	19	4503	18	Dominated (monthly)
Non-severe infection given severe leukopenia						

in monthly monitoring arm						
	0.01	1581	19	3119	18	Dominated (monthly)
	0.4	1581	19	1248	18	1260
Survival in patients with severe infection given severe leukopenia in monthly monitoring arm						
	0.86	1581	19	2067	18	Dominated (monthly)
	0.99	1581	19	2072	18	Dominated (monthly)

*Dominated (monthly) indicates that the monthly strategy is dominated by the weekly strategy. This means that the monthly strategy is both more costly and less effective compared to the weekly strategy.

Table 14. Results of sensitivity analyses on probabilities of clinical parameters in the decision tree

Cost Parameter	**Cost Range ($)**	**Cost per patient, weekly CBC monitoring ($)**	**Effectiveness per patient, weekly monitoring (QALY)**	**Cost per patient, monthly CBC monitoring ($)**	**Effectiveness per patient, monthly monitoring (QALY)**	**Marginal cost / QALY ($)**
Baseline		1581	18.74	2070	18.52	Dominated (monthly) *
Weekly CBC						
	120	921	19	2070	18	Dominated (monthly)
	1200	2001	19	2070	18	Dominated (monthly)
Three months						

CYC						
	250	1360	19	1853	18	Dominated (monthly)
	650	1759	19	2244	18	Dominated (monthly)
Outpatient physician visit						
	50	1381	19	1866	18	Dominated (monthly)
	250	1782	19	2275	18	Dominated (monthly)
Emergency room visit						
	500	1581	19	2053	18	Dominated (monthly)
	1500	1582	19	2075	18	Dominated (monthly)
Sepsis						
	20000	1565	19	1480	18	285
	100000	1613	19	3209	18	Dominated (monthly)
Outpatient antibiotics						
	10	1581	19	2069	18	Dominated (monthly)
	120	1582	19	2072	18	Dominated (monthly)
Monthly CBC						
	30	1581	19	1915	18	Dominated (monthly)
	300	1581	19	2185	18	Dominated (monthly)

*Dominated (monthly) indicates that the monthly strategy is dominated by the weekly strategy. This means that the monthly strategy is both more costly and less effective compared to the weekly strategy.

Table 15. Results of sensitivity analyses on cost parameters in the decision tree for the CEA

Variable (Q0L)	Value	Range of Utility (QoL)	Cost per patient, weekly CBC monitoring ($)	Cost per patient, monthly CBC monitoring ($)	Marginal cost/QALY ($)
Baseline			1581	2070	Dominated (monthly)*
Baseline quality of life	0.7	0.6	1581	2070	Dominated (monthly)
		0.9	1581	2070	Dominated (monthly)
No leukopenia in weekly arm	1.0				
		0.9	1581	2070	390
		1.0	1581	2070	Dominated (monthly)
Non-severe leukopenia in weekly arm	0.96				
		0.94	1581	2070	Dominated (monthly)
		0.99	1581	2070	Dominated (monthly)
No infection given severe leukopenia in weekly arm	1.0				
		0.9	1581	2070	Dominated (monthly)
		1.0	1581	2070	Dominated (monthly)

Non-severe infection given severe leukopenia in weekly arm	0.96				
		0.94	1581	2070	Dominated (monthly)
		0.99	1581	2070	Dominated (monthly)
Sepsis given severe leukopenia in weekly arm	0.8				
		0.7	1581	2070	Dominated (monthly)
		0.99	1581	2070	Dominated (monthly)
No leukopenia in monthly arm	1.0				
		0.9	1581	2070	Dominated (monthly)
		1.0	1581	2070	235
Non-severe leukopenia in monthly arm	0.96				
		0.94	1581	2070	Dominated (monthly)
		0.99	1581	2070	254
No infection given severe leukopenia in monthly arm	1.0				
		0.9	1581	2070	Dominated (monthly)
		1.0	1581	2070	717

Non-severe infection given severe leukopenia in monthly arm	0.96				
		0.94	1581	2070	Dominated (monthly)
		0.99	1581	2070	Dominated (monthly)
Sepsis given severe leukopenia in monthly arm	0.8				
		0.7	1581	2070	Dominated (monthly)
		0.99	1581	2070	Dominated (monthly)

Parameter	**Value (years)**	**Range**	**Cost per patient, weekly CBC monitoring ($)**	**Cost per patient, monthly CBC monitoring ($)**	**Marginal cost/QALY ($)**
Life expectancy	27	7	1581	2070	Dominated (monthly)
		37	1581	2070	Dominated (monthly)

*Dominated (monthly) indicates that the monthly strategy is dominated by the weekly strategy. This means that the monthly strategy is both more costly and less effective compared to the weekly strategy.

Table 16. Results of sensitivity analyses of quality of life and life expectancy and parameters in the decision tree for CEA

Probabilistic sensitivity analysis

The probabilistic sensitivity analyses (PSA) supports the dominance of the weekly CBC strategy over the monthly CBC strategy. The graph of the acceptability curve is generated by PSA based on the net benefits of either strategy at each willingness-to-pay threshold is shown in Figure 2. This curve reflects the changing percentage of iterations for which a certain strategy is cost-effective relative to the other strategy. The fact that the line connecting the open triangles (weekly CBC) is always above the line connecting the filled triangles (monthly CBC) indicates that the weekly CBC strategy dominates the monthly CBC strategy over the whole range of the WTP threshold.

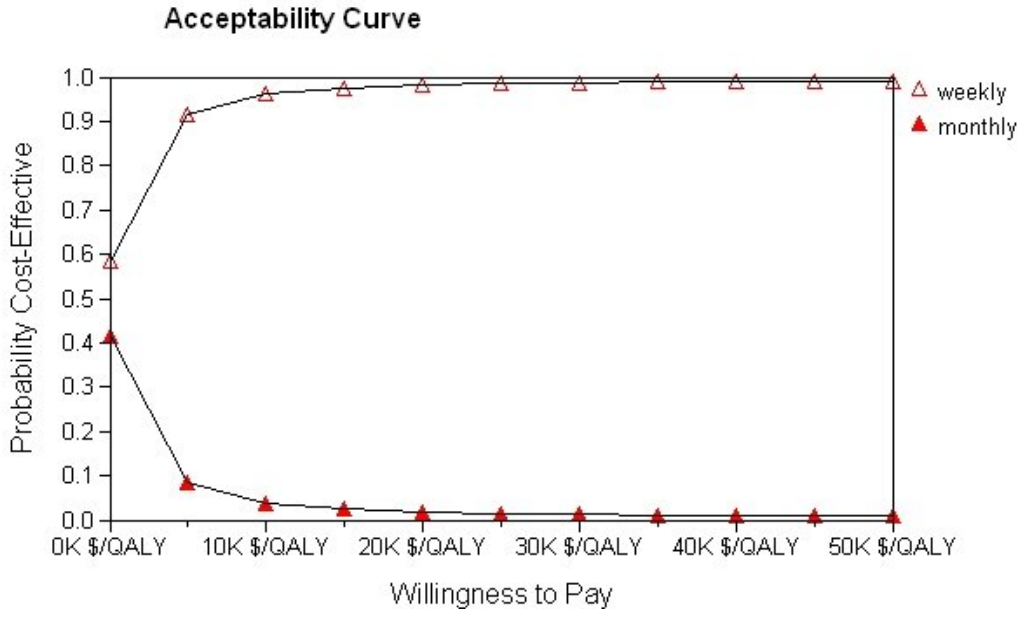

Figure 2. Acceptability curve of the cost-effectiveness of weekly and monthly CBC monitoring strategies according to willingness to pay (WTP). The vertical axis represents the probability that the weekly CBC strategy is cost effective compared to the monthly CBC strategy for that particular trial attempt of the analysis and the

horizontal axis represents the willingness to pay threshold. The current graph was generated based on 1000 trials conducted for the PSA.

DISCUSSION

Cost-Effectiveness Analysis

Basic concepts[48]

CEA is a technique for selecting among competing strategies wherever resources are limited. In healthcare, CEA is used to compare the relative value of various clinical strategies. A new strategy is compared with the existing strategy to generate a cost-effectiveness ratio. The units of measurement in CEA are the marginal (incremental) costs and benefits. The common measure of excess cost attributable to the new strategy is called the incremental cost-effectiveness ratio (ICER) and is calculated as:

$$\frac{\text{Cost strategy A} - \text{Cost strategy B}}{\text{Effectiveness strategy A} - \text{Effectiveness strategy B}}$$

The ICER might be considered the price of one additional outcome purchased by switching from the existing strategy to the new strategy. If the price is low enough [below the arbitrary preset amount called the willingness to pay (WTP) threshold], the new strategy is considered cost effective. The numerator of the ICER calculation in addition to costs of the strategies can also include averted disease costs. The typical WTP threshold used in multiple studies is $ 50000, however this is not absolute and has been varied and even questioned as possibly lower than the optimal value[49]. Quality Adjusted Life Years (QALY) is the most widespread method of measuring the value of providing a healthcare intervention and it reflects both the quality and quantity of life[50]. This is also the recommended measure of effectiveness by the United States Public Health Services Task Force (1996).

A cost effective strategy is one that has good value. Cost effectiveness is a value judgment, as the willingness to pay is arbitrarily set and depends on available financial resources. Decision-making related to CEA results can be thought of as a 2 X 2 table of cost versus effectiveness as shown below. CEA is pertinent only to situations in which the new strategy is both more effective and costly or both less effective and costly (cells A and D of the 2 X 2 table). In situations where the new strategy is more expensive but less effective, the strategy is considered dominated and in situations where the new strategy is less costly but more effective is considered to dominate the other strategy.

	Less effective	More effective
Less expensive	Cost effectiveness analysis	Dominating
More expensive	Dominated	Cost effectiveness analysis

Fig 3. Two by two table of cost and effectiveness.

Discussion specific to present study

We analyzed the cost effectiveness of weekly WBC monitoring at preventing serious infection/sepsis as a consequence of leukopenia in patients with GPA on CYC in the present study. It is well accepted that the development of sepsis has a significant impact on the quality of life (QoL) for survivors, which in this case would compound the existing morbidity from underlying GPA. The baseline cost effectiveness analysis

shows that the strategy of weekly CBC monitoring dominated (was less expensive and more effective) the strategy of monthly CBC monitoring.

However, under certain circumstances, the weekly CBC strategy was associated with greater cost and equal or greater effectiveness than the monthly CBC monitoring. One of these circumstances in which the weekly strategy would also offer more effectiveness at a greater cost if less than 16% patients currently on monthly CBC testing developed severe leukopenia. The current literature reveals that severe leukopenia may occur in up to 60% patients[13] on monthly CBC monitoring strategy and therefore this is a clinically unlikely scenario. If over 48% patients on monthly CBC monitoring develop non-severe leukopenia, the weekly strategy is more expensive and more effective likely because checking weekly CBC may be helpful in detecting severe leukopenia (progressing from non-severe leukopenia) earlier if and when it occurs. The other scenarios such as if ≥ 90% patients on monthly CBC monitoring would develop no infections, if ≤ 7.5% patients in the monthly CBC arm would develop severe infections are also clinically unlikely based on currently known frequencies of these events in literature. If more than 26% patients in the monthly CBC arm were to develop non-severe infections, weekly CBC monitoring would be more expensive but also more effective as this reflects a patient population theoretically likely to develop severe infections *de novo* or as a continuum of the non-severe infection. If more than 30% patients on weekly CBC monitoring develop non-severe leukopenia, switching over to monthly CBC appears more expensive but equally effective. This would suggest that maintaining the weekly strategy in these patients costs less but equally effective (would likely detect progression to severe leukopenia) and if therefore to be recommended. Based on the available literature on

the occurrence of non-severe leukopenia and experience with CYC[8] this observation is unlikely in clinical practice.

If the cost parameters are studied, one situation where the weekly strategy offers increased cost as well as effectiveness is if the cost of sepsis management was less than $27000. This is inconsistent with currently available costs. Moreover, even if the management of sepsis were cheaper than present as envisioned in the scenario, it would still be prudent to switch over to a weekly CBC monitoring to potentially avoid future infectious complications.

If a patient with GPA on weekly CBC monitoring has a slightly lower quality of life and continues to experience freedom from leukopenia or experience non-severe leukopenia, switching to a monthly strategy appears to be more effective but also more expensive based on this CEA model. A lower quality of life in this case may reflect damage from previous systemic inflammation. Since patients in the CCF GPA database have had repeated therapy CYC for severe flares of GPA, they may theoretically have accumulated more damage from the previous systemic inflammation. However, given the cumulative bone marrow toxicity from repeated treatment or prolonged treatment with CYC, this cannot be recommended in practice. The PSA Monte Carlo analysis supports the finding of the baseline CEA that the weekly CBC strategy dominates the monthly CBC strategy. Even at the upper extreme of willingness to pay threshold ($50000), the weekly CBC strategy is cost effective compared to the monthly CBC monitoring strategy. This supports the observed results of the baseline CEA analysis.

The quality of the available literature determined the quality of data available to generate probabilities for the decision tree analysis. Most of the mean probabilities and ranges for sensitivity analyses (deterministic and probabilistic) were derived from the CCF GPA database and randomized controlled trials using daily oral CYC for patients with severe GPA similar to patients in the CCF GPA database. These were multicenter trials performed in the US and Europe and form the key trials that have advanced our understanding regarding the management of patients with GPA. The quality of the data therefore is the best that can be obtained at the present time. It was also attempted to include studies with most possible clear documentation of the relationship between severe infection and severe leukopenia. In the weekly group, the CCF GPA database provided the clearest possible documentation of this relationship whereas for studies included in the monthly group, the included studies suggested this relationship. Although the main criteria used to select studies for inclusion in the analysis were patients with severe GPA on daily oral CYC, inherent differences regarding susceptibility to leukopenia and infection possibly exist between patients in our cohort and other included studies. The only probabilities that were entered by consensus were the probability of "no leukopenia" and "no infection given severe leukopenia" and "non severe leukopenia in patients" in the weekly CBC monitoring arm as they are not reported routinely in manuscripts publishing the results of these trials. However, we subjected these probabilities to sensitivity analyses using wide ranges (0.01 – 0.99) to account for the fact that these were consensus assumptions of the mean probability estimates. This also makes the results of the analyses more valid but less robust than they would have been with available data. One of the other limitations of the analysis is that a simplistic decision analysis tree was constructed given that detailed decision-making regarding changes in CYC dosing upon

development were not available in the published literature. Following the development of leukopenia, the dose of CYC may be decreased, the CYC may be temporarily or permanently withheld or the patient's immunosuppression regimen switched to another medication. Although we had this information from the CCF GPA database, this was not available for other studies in the literature. Another caveat that should be borne in mind is that most of these studies, the relationship between severe infection and severe leukopenia is not explicitly documented, although these are reported in the same time period that the patients were on oral CYC. However, as discussed earlier, we believe that severe leukopenia does occur in patients on CYC, but this does not constitute the only risk factor for infection in these patients, especially during the induction phase of immunosuppression when they are on concomitant high dose glucocorticoids as were patients in the CCF GPA database (median dose 35 mg daily). Measuring WBC counts is therefore one assessable aspect of leukocytes that is easy to measure and has been shown to have a relationship to infection. The quality of life estimates are also derived from the best available limited literature regarding patients with GPA.

The strategies compared in this analysis are extremely pertinent to management of patients with GPA. We chose the monthly and weekly CBC as frequencies as these appear to be the most common monitoring frequencies observed in practice. The costs and QALY data were obtained from the public healthcare databases, which are the best available sources for this information. Even with this information, the external validity of the results of the analyses is still uncertain due to the influence of multiple variables in the analysis.

This is the first cost effectiveness analysis of CBC monitoring strategies for CYC toxicity in patients with severe GPA. We therefore have no prior studies to compare

our results directly with. Two of the many possible reasons for the lack of studies in this area are the rarity of disease (the prevalence of GPA is 1-3 per 100,000) and the managing physicians' personal preference and experience with a particular CBC monitoring strategy. Complete blood count is a simple and relatively non-expensive test and probably undervalued in the clinical management of patients with GPA. Although the results of a CBC test have limited diagnostic value, they are invaluable in providing very early insights into potential toxicity from CYC or other immunosuppressant use. Given that GPA tends to be a relapsing disease, and the potential for re-treatment with CYC for severe flares/relapses, bone marrow toxicity is a legitimate concern. A significantly decreasing trend of WBC count or severe leukopenia may therefore provide a window of opportunity for appropriate intervention regarding CYC.

The incremental cost-effectiveness ratios (ICERs) in the results of the analyses (including the clinically improbable scenarios) are below the typically accepted willingness to pap (WTP) threshold, which is typically set at $50000. This should however, not invoke a sense of complacency and the non-financial consequences of severe leukopenia and consequent severe infection and potential morbidity and mortality should be factored into decision making regarding the choice of strategy for frequency of CBC monitoring in these patients. As noted above, the additional loss of quality of life from a severe infection/sepsis to the pre-existing compromised quality of life from GPA is significant for many patients in their productive years.

CONCLUSIONS

Weekly CBC monitoring for surveillance for leukopenia and potential consequences (infection and mortality) in patients with GPA on daily CYC appears cost effective compared with monthly CBC monitoring based on the current analysis, but these results are influenced by multiple uncertainties and need verification with future studies. Ideally, a prospective study in a comparable cohort of patients with GPA with weekly and monthly CBC monitoring and careful data collection regarding leukopenia and infection is probably the best way to validate our observations. This CEA provides direction for further studies in this area and similar research in patients with other forms of vasculitides and other rare diseases. However, we appreciate that the concept of "cost-effectiveness" is a value judgment. In this analysis, we used a WTP threshold of $50,000 but we leave it to the individual reader to assess on a personal level whether the use of weekly CBC measurement is "cost-effective". We suggest that considerations other than costs associated with consequences of severe leukopenia such as quality of life be factored into this decision-making. However, as noted above, we do not have all the probabilities reported in literature and some were derived by consensus. Given these uncertainties, we feel that there is a potential need for cost effectiveness studies of interventions in patients with rare diseases. The better documentation of occurrence, severity and absence of events such as leukopenia and infection while on CYC will aid the performance of a more robust CEA with more reliability and greater applicability for these patients.

APPENDIX

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