Rapid paper

Key considerations for modelling the long-term costs and benefits of treatments for ANCA-associated vasculitis

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ABSTRACT

Objective. *Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of severe and chronic autoimmune diseases. Patients undergo two treatment phases: inducing remission and maintaining remission to prevent organ damage. Immunosuppressants, including glucocorticoids (GCs) are used as first-line treatment, but long-term GC use is associated with toxic effects. Novel treatments reduce or replace the need for long-term GC, and therefore can reduce GC-related toxicity. The evolving treatment landscape has presented new challenges for health technology assessment (HTA) of new treatments in AAV and long-term modelling of costs and outcomes in this disease.*

Methods. *Using the appraisal of avacopan in England (NICE) as a case study, this paper aims to identify the key challenges involved in the economic evaluation of new treatments for AAV, with a particular focus on the long-term modelling of the treatment costs and benefits for the purpose of HTA. The outcome of this study is a set of recommendations for modelling the cost-effectiveness of new treatments for AAV from the HTA perspective.*

Results. *The discussion focuses on the appropriate model structure, approach to modelling end-stage renal disease (ESRD) as a key determinant of cost-effectiveness, capturing the impact of GC-related adverse events, and estimation of short and long-term costs of AAV.*

Conclusion. *Economic evaluation of new treatments for AAV needs to capture all relevant downstream effects. ESRD is a key driver of cost-effectiveness but is associated with major uncertainty. Future observational studies need to offer sufficient detail to allow for differentiation in event rates across treatment options.*

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a collection of relatively rare and often life-threatening autoimmune diseases that cause inflammation and necrosis to small and medium blood vessels, particularly those in the respiratory and renal systems (1). Renal involvement is the most common severe manifestation, among all organ damages caused by AAV, leading to the development of end-stage renal disease (ESRD) in some patients (2).

Treatment for AAV comprises induction therapy to achieve remission and maintenance therapy to sustain remission. The current standard of care (SoC) treatments recommended for induction therapy in patients with newly diagnosed or relapsing AAV include a combination of glucocorticoids and either cyclophosphamide or rituximab (3). Patients are treated with maintenance therapy to prevent relapse using azathioprine, mycophenolate mofetil, methotrexate, or rituximab. Patients experiencing a relapse undergo re-induction therapy with glucocorticoids and either cyclophosphamide or rituximab. Overall survival remains poor for patients with AAV, despite treatment. Patients who are on high-dose glucocorticoids suffer from morbidity associated with treatment toxicity (4). In particular, glucocorticoid-driven infections is a major driver of mortality, and there is a significant unmet need for effective steroid sparing treatment strategies (5). Avacopan is an orally administered complement 5a receptor (C5aR1) antagonist that inhibits C5a-mediated neutrophil activation. Based on the AD-VOCATE randomised control phase III trial (6), avacopan was non-inferior to prednisone taper in achieving remission, and superior for sustaining remis-

sion at week 52, making it an effective treatment option for AAV which reduces or avoids the use of glucocorticoids, and has been recommended by the National Institute for Health and Care Excellence (NICE) for treating severe active AAV in adults (7).

The addition of new treatment options for AAV presents new challenges for health technology assessment (HTA) for estimating long-term costs and effects in this disease. The objective of this publication is to identify the key challenges involved in the economic evaluation of new treatments for AAV, using the recent NICE Technology Appraisal Guidance for avacopan for patients with severe and active AAV (TA825) (7) as a case study.

Methods

Model characteristics and structure

An economic model framework needs to capture the full impact on costs and outcomes of introducing a new treatment (8). In AAV, the key determinants of treatment success are achieving remission, and preventing relapse and its consequences. A Markov model framework with discrete health states representing disease remission, relapse, and other relevant health states (including ESRD), such as the example presented in Figure 1, can capture the effect of treatment over a lifetime horizon, and is suitable for this purpose, as established by NICE in two previous technology appraisals for this indication (7, 9). The model cycle length should be sufficiently short to reflect the schedule of treatments and the rapid progression of AAV.

Treatments

The selection of treatments in the model should follow the clinical guidelines of the target country. In the case of England, the selection of intervention and comparators in the model should align with NICE guidance (7). This includes avacopan in combination with cyclophosphamide or rituximab, with the option to use prednisone as the first line therapy for the induction of remission in AAV. It should be assumed that the length of treatment with avacopan is 52 weeks, in the absence of evidence

of effectiveness of treatment beyond 52 weeks. After the induction phase, the treatment mix is uncertain, and should follow clinical recommendations of the target country for the economic model. As an example, maintenance therapy with rituximab is not routinely commissioned in England, and clinical experts in TA825 advised that 30-40% of patients who have received prior rituximab treatment are considered for rituximab maintenance treatment upon reaching remission (7).

Modelling relapse and remission

The modelling of relapse and remission phases should be in line with the accepted definitions used in clinical practice, as suggested in Table I. The number of relapses which can occur in the model can be limited to reduce model complexity. For example, in the company submission for TA825, the model was restricted to a maximum of three induction phases (equivalent to two relapses).

Modelling ESRD

A major difference between the economic models presented by the manufacturers in TA308 and TA825 is the inclusion in the latter model of a separate health state to represent ESRD as a severe complication of worsening renal function due to AAV (10). Treatment for ESRD represents a significant burden on patients and the healthcare system, due to the need for chronic renal replacement therapy or renal transplant. The probability of developing ESRD should be linked to relapse, a known predictive independent risk factor, and ideally should be modelled explicitly via changes in estimated glomerular filtration rate (eGFR) informed by clinical trial data. The baseline hazard rate used in the model should reflect the incidence of ESRD observed in real-world studies in AAV, following the method used in TA825. The decline in eGFR due to disease relapse should be derived from observed trial data or real-world data. In the absence of studies, clinical expert opinion may be used, as was the case with the economic model in TA825, with comprehensive sensitivity analyses to gauge uncertainty. Based on clinical expert advice, the decline in eGFR after

each relapse is in the range from 10 ml/min/1.73m^2 to 20 ml/min/1.73m^2.

The decline in eGFR with each relapse can be linked to the probability of ESRD based on published observational studies. In TA825, the committee considered multiple sources (11-13), and concluded that estimates based on individual studies as well as a pooled estimate produced by the evidence review group (ERG) were considered valid. It must be noted that the pooled approach is associated with limitations and a risk of bias, due to the fact that estimated coefficients obtained from multiple Cox proportional hazards models that each adjust for a different set of covariates are inconsistent (14). The hazard ratios from the studies considered by NICE are reported in Table I.

Modelling adverse events of glucocorticoids

Treatment with glucocorticoids is associated with severe adverse events (AEs), which includes, but is not limited to, infections, osteoporosis, heart disease and diabetes (4, 15). Severe infections attributed to the use of glucocorticoids have been reported in 44% of patients with AAV over 4 years, with the majority occurring during the first two years of treatment (15) and are the cause of around a half of all deaths in the first year following AAV diagnosis (16). It is therefore important to account for the impact of both short-term AEs on cost and patient outcomes (which can be informed by trial follow-up), and late effects of glucocorticoid use based on real-world evidence sources or published literature.

Cost of managing AAV

Patients with severe and active AAV have a high risk of hospital admission due to complications of AAV and associated treatments. The mean length of stay for patients in the SoC arm of the ADVOCATE trial was 19.6 days (corresponding to a mean cost of £5,802 per patient), compared against 13.8 days and a mean cost of £2,948 in the avacopan arm (7). The difference was attributed to fewer relapses and complications of glucocorticoid treatment in the avacopan arm. Economic evalu-
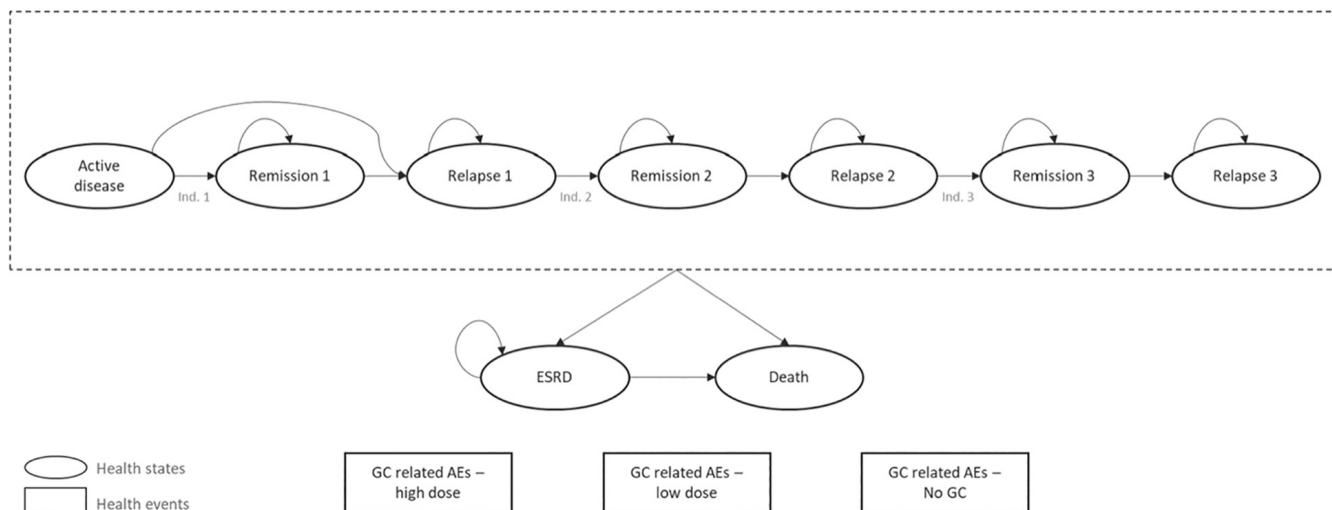
Fig. 1. Model structure.

Table I. Recommendations for key inputs in the economic model

Input/assumption	Recommendation
Definition of health states	
Definition of relapse and remission	Accepted definition used in clinical guidelines or pivotal randomized control trials: *e.g.*, in the ADVOCATE trial, remission was defined as achieving a Birmingham Vasculitis Activity Score (BVAS) of zero and not taking glucocorticoids within 4 weeks of the end of the 6-month induction period. In the same study, relapse was defined as worsening of disease measured using the BVAS, after having previously achieved remission (6).
ESRD	eGFR<15ml/min/1.73m^2 and present a chronic need for RRT.
ESRD	
Probability of ESRD	Should be linked to relapse and remission of AAV via progression of eGFR.
Impact of relapse on eGFR	Should be estimated based on published trial or observational data. In the absence of study data, use assumptions validated by clinical experts. Based on TA825 economic model, eGFR declines after each relapse by 10-20ml.
Effect of eGFR decline on probability of ESRD	Based on published studies, the hazard ratio for each point increase in eGFR ranges from 0.9 to 0.96. This was based on Gercik *et al*. (12) and Gopaluni *et al*. (13), both of which reported HR=0.9, Brix *et al*. (HR=0.96) (11) and a pooled estimate of the Gercik *et al*. and Brix *et al*. studies used by the ERG in TA825 (HR=0.95). The NICE committee considered that it is relevant to consider the hazard ratios reported by the individual studies, as well as the pooled estimated produced by the ERG.
Adverse events	
Short-term AEs	Short-term adverse events of treatments (particularly of GCs) should be informed based on trial data, *e.g.* ADVOCATE.
Late effects of GCs	The model needs to account for long-term consequences of GCs over a lifetime horizon, including diabetes, cardiovascular disease, osteoporosis. This is especially relevant when evaluating treatments which can reduce or avoid GC use, such as avacopan.

ations of treatments of AAV should appropriately capture the significant cost burden of inpatient hospital admissions. In their report for the TA825 appraisal, the ERG noted that total healthcare cost estimated in the economic analysis was substantially lower compared to the cost reported in real-world data in the UK. It may be possible that the modelling approach missed out co-morbidities or other hidden costs linked to AAV. Given that the lifetime cost of treatment for AAV represents a sub-stantial burden to health systems, it is important to capture all relevant downstream costs which may be reduced through the use of effective treatments.

Conclusions
Health economic modelling should capture all key clinical and cost events that occur for patients over the course of the disease, in line with international good practice guidelines (8). In the case of AAV, the key factors which influence clinical outcomes and costs for patients, and are likely to be key differentiators between treatments, are the probability of remission, relapse, ESRD and complications of disease, and AEs of treatments, especially glucocorticoids. The outcome of this discussion paper is a set of recommendations intended as a guide for authors of future cost-effectiveness studies for treatments in AAV (Table I).

Appropriate modelling of ESRD is essential, as a key driver of survival, quality of life, and cost of treatment over a

lifetime. However, significant evidence gaps remain and key assumptions for the progression of patients to ESRD require validation. In particular, a prospective or well-designed retrospective study is needed to estimate the impact of relapse on eGFR.

Granular disease registry or claims data are needed to capture the late complications of AAV and treatments which are not captured within the short horizon of randomised controlled trials, in particular AEs linked to the use of glucocorticoids. The data needs to be sufficiently detailed to allow differentiation in the incidence of AEs by treatment. A key limitation of retrospective cohort studies is that they do not report sufficient detail to determine the relative safety of different treatments for AAV.

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