Voclosporin and Belimumab for Lupus Nephritis

Revised Background and Scope

September 29, 2020

Background

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with an estimated prevalence of 300,000 to 1.5 million Americans.[1] It is more common in women (90% of diagnosed cases) and in non-Whites (four times higher prevalence in Blacks, two times higher prevalence in Hispanics). Approximately 50-60% of patients with SLE will be diagnosed with lupus nephritis (LN), a heterogenous disease characterized by inflammation in the glomeruli leading to proteinuria and an active urinary sediment.[2,3] LN is more common among men with SLE and typically arises in the third or fourth decade of life.[4,5] The diagnosis is suspected when there is excess protein in the urine and made with a kidney biopsy. Within 15 years of the diagnosis, between 10% to 30% of patients with LN progress to end stage renal disease (ESRD), requiring dialysis or kidney transplantation [6-8] The prognosis of patients with LN is worse in Blacks and Hispanics.[9,10]

LN is divided into six classes based on the percentage of glomeruli affected and the pathological spectrum of the lesions seen on biopsy (Table 1).[11] Even though LN is one of the primary causes of death and disability in patients with SLE, there are no drugs with an FDA indication for LN. Guidelines typically do not recommend treatment of Class I or II LN because of the toxicity of treatment and the lack of clear markers to identify who will progress to more severe disease. For patients with Class III-V, guidelines recommend induction therapy with high dose corticosteroids combined with either mycophenolate mofetil (MMF) or cyclophosphamide, followed by maintenance therapy with MMF.[12,13] Other treatments sometimes added to this background therapy include rituximab and tacrolimus. Unfortunately, fewer than 50% of patients with LN respond to current combination therapy, so there is a large unmet need for new therapies.

Table 1.1. Classification of Lupus Nephritis

Class I	Minimal Mesangial LN		
Class II	Mesangial Proliferative LN		
Class III	Focal LN (<50% glomeruli)	III (A)	Active Lesions
		III (A/C)	Active and Chronic Lesions
		III (C)	Chronic Lesions
Class IV	Diffuse LN (≥50% glomeruli)	IV (S)	Diffuse Segmental
		IV (G)	Diffuse Global
		IV (A)	Active Lesions
		IV (A/C)	Active and Chronic Lesions
		IV (C)	Chronic Lesions
Class V	Membranous LN		
Class VI	Advanced Sclerosed (≥90% glomeruli)		

There are two emerging therapies for LN currently under consideration by the FDA. The first, voclosporin, is a novel calcineurin inhibitor. The second, belimumab (Benlysta), is a B-cell activating factor inhibitor that has been previously approved for the treatment of SLE, but has not received a label for LN.

Stakeholder Input

This scoping document was developed with input from diverse stakeholders, including patient organizations, advocacy groups, clinical experts, clinical societies, and manufacturers of the drugs under review. This document incorporates feedback gathered during calls with stakeholders, open input submissions from the public, and public comments on our draft scoping document. ICER looks forward to continued engagement with stakeholders throughout its review to refine our understanding of the clinical effectiveness and value of voclosporin and belimumab.

One important source of patient input comes from a meeting convened in 2018 by the Lupus and Allied Diseases Association, the Lupus Foundation of America, and the Lupus Research Alliance. The purpose of this meeting was to elicit the perspectives of patients living with lupus as part of the FDA's Patient Focused Drug Development Initiative. Insights from the meeting are summarized in the report *Lupus: Patient Voices*.[14] In the report, patients with LN reported that the symptoms that most negatively affected their lives were fatigue (24%), joint and muscle pain (24%) and their kidney disease (21%). Among all patients with SLE the top three downsides of their current treatment were side effects (54%), the number of pills and other treatments taken each day (54%), and the cost of treatment (42%).[14]

Feedback from patients highlighted the importance of steroid-sparing as an outcome because of the manifold significant long-term harms from corticosteroids including diabetes, osteoporosis and

the associated fractures, hypertension, obesity, infections, cataracts, mental health issues and so on. We also heard that we should place greater emphasis on the outcomes that matter most to all lupus patients: fatigue, joint and muscle pain, and kidney disease. Finally, we also heard about the impact of lupus nephritis and the drugs used to treat it on childbearing potential.

We also heard repeatedly about the excess impact that LN has on communities of color including those of African descent, LatinX, and Asians. The feedback emphasized the importance of doing subgroup analyses in these patient populations.

One current concern for patients is the route of administration of therapies for LN. Given the COVID-19 pandemic, patients are understandably concerned about needing to come into infusion centers for therapies that require intravenous infusion. We also heard that step therapy restrictions present frustrations for both patients and their providers, particularly when they have adverse reactions to a generic form of a drug. They also highlighted issues with access to care in general and in particular for patients in rural areas.

Given the young age of onset of LN, the disease has a huge impact on patients' ability to work and to advance in their careers. It is a huge burden to bear.

Report Aim

This project will evaluate the health and economic outcomes of voclosporin and belimumab for LN. The ICER value assessment framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting,

we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of focus for the review is adult patients with Class III, IV, or V LN ages 18 and older.

Interventions

The full list of interventions is as follows:

- Voclosporin plus standard therapy
- Belimumab (Benlysta) plus standard therapy (defined below)

Comparators

Data permitting, we intend to compare voclosporin and belimumab to each other and to standard therapy, defined as mycophenolate mofetil (MMF) plus corticosteroids or cyclophosphamide plus corticosteroids.

Outcomes

Unfortunately, there is no standard outcome for clinical trials in lupus nephritis. Recently, there is growing consensus that low proteinuria (<0.7-0.8 mg) with preserved renal function predicts good renal outcomes over the long term and that a clean urinary sediment is not essential.[15] This may in part explain the change in the primary outcome in the pivotal trial of belimumab for lupus nephritis.

As noted in the background, there is clinical heterogeneity in both presentation and response to therapy by race and ethnicity, so we will perform subgroup analyses by race and ethnicity where possible.

The outcomes of interest are described in the list below:

- Patient-Important Outcomes
    - Complete renal remission (normal renal function) at one year*
    - Maintenance of remission
    - Reduction in corticosteroid dose (steroid sparing)
    - Reduction in renal flares
    - Prevention of chronic kidney disease
    - Dialysis

    - Renal transplant
    - Fatigue
    - Joint and muscle pain
    - Childbearing potential
    - Adverse events (AEs) including
        - Significant adverse events
        - Adverse events leading to drug discontinuation
        - Infections
        - Acute renal failure
        - Diabetes
        - Hypertension
        - Nephrotoxicity
        - Neurotoxicity (encephalopathy, tremors, headache, seizures)
        - Progressive multifocal leukoencephalopathy (PML)
        - Hypersensitivity reactions
        - Infusion reactions
        - Depression
        - Suicide
        - Gastrointestinal (nausea, diarrhea)
        - Death
- Other Outcomes
    - Renal response
    - Partial renal response
    - Duration of complete renal response
    - 24-hour urine protein excretion (<0.25, 0.25-3.0, >3.0 g/day)
    - Change in creatinine
    - Change in estimated glomerular filtration rate (eGFR)
    - The proportion of patients with eGFR >90, 60-89, 30-59, 15-29, <15
    - Change in urine protein creatinine ratio (UPCR)
    - The proportion of patients with UPCR by categories
    - Change in serum albumin
    - Change in complement levels
    - Change in ANA level
    - Change in DS DNA level
    - Change in Quality of Life
    - SELENA-SLEDAI score

*Prospective cohort data have confirmed that proteinuria < 0.7 to 0.8 g/day at 12 months is the best predictor of good renal outcomes at 10 years.[15-18]

Timing

Evidence on intervention effectiveness will be derived from studies of at least 24 weeks duration and evidence on harms from studies of at least 24 weeks duration, though studies of at least one-year duration are preferred.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the United States.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.2. Potential Other Benefits or Disadvantages and Contextual Considerations

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic.		Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic.
Very similar mechanism of action to that of other active treatments.		New mechanism of action compared to that of other active treatments.
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials.		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials.
The intervention offers no special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.		The intervention offers special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.
This intervention will not differentially benefit a historically disadvantaged or underserved community.		This intervention will differentially benefit a historically disadvantaged or underserved community.
Small health loss without this treatment as measured by absolute QALY shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.
Small health loss without this treatment as measured by proportional QALY shortfall.		Substantial health loss without this treatment as measured by proportional QALY shortfall.
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.
Will not have a significant impact on improving return to work and/or overall productivity vs. the comparator.		Will have a significant impact on improving return to work and/or overall productivity vs. the comparator.
Other		Other

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

We received input highlighting that LN impacts non-white race/ethnicity subgroups disproportionately, so there is the potential for differential benefits. In addition, LN occurs in the prime working years and thus has a significant impact on productivity and also has a significant impact on caregiver productivity and quality of life.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost effectiveness of the treatments of interest relative to relevant comparator treatments. The target population will consist of adult patients (18 years old or older) with LN Class III, IV, or V.

The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate modified societal analysis. Following the value assessment framework protocol, this modified societal perspective analysis will be considered as a co-base case if the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial.

The model will be based on one of the possible model structures for LN identified in the published literature. One option is a structure based on health states such as active disease, complete renal remission, partial renal remission, ESRD, and death.[19-22] The other option is a multi-state model with health states based on eGFR states, proteinuria states, ESRD, and death.[23-25]. The third option is a model based only on proteinuria states, ESRD, and death; this structure is possible considering proteinuria as the main predictor for disease progression. ICER preferred approach is either the second or third option of modeling. This preference is argued by (a) reliability of data informing the long-term progression of the disease; (b) possibility to model patients with difference severity of the disease at induction therapy, (c) possibility to model the progression of the disease by ethnicity. A cohort of patients will transition between states during predetermined cycles (anticipated to be six months during the trials duration, and then every 12 months) over a lifetime time horizon, modeling patients from treatment initiation until death.

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying cost effectiveness between interventions. Treatment effectiveness will be estimated using data from the pivotal trials for voclosporin and belimumab.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, AEs, and direct medical costs. The health outcome of each intervention will be evaluated in terms of averted clinical cases (such as number of relapses avoided, number of patients avoiding ESRD, number of patients avoiding dialysis, number of kidney transplants avoided) as well as clinical benefits (such as number of patients achieving remission), life-years gained, quality-adjusted life years (QALYs) gained, and equal value life years gained (evLYG). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity changes and other indirect costs will be included in a separate analysis as available

data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life-year gained, cost per relapse avoided, cost per ESRD avoided, and cost per remission gained.

Several stakeholders inquired on a subgroup analysis by race/ethnicity to quantify the benefit in key population subgroups. Considering limited information in the published literature, ICER will request manufacturers to provide data by ethnicity. We will also strive to include quality of life weights that were collected from populations that reflect the race/ethnicity prevalence of the overall LN population. ICER will also consider including a wider impact of the disease progression in modelling (e.g., childbearing potential by the disease progression) if data on such relationships can be obtained.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This potential budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

As described in its Value Assessment Framework for 2020-2023, ICER will include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by voclosporin or belimumab (e.g., dialysis, renal transplant), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of LN beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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