

Statement from the Regional HTA Centre of Region Västra Götaland, Sweden

Eculizumab treatment in paroxysmal nocturnal hemoglobinuria (PNH)

Question at issue

Is treatment with eculizumab in PNH patients better than standard treatment with blood transfusions and if indicated anticoagulation?

PICO (Patient, Intervention, Comparison, Outcome)

- P = Patients, all ages, with classic paroxysmal nocturnal hemoglobinuria (PNH), diagnosed by immunophenotyping
I = Treatment with Eculizumab (Soliris ®)
C= Standard Treatment only or standard treatment + placebo injections
O = Primary outcome:
Mortality

Secondary outcomes:

Transfusion Requirements,
Thromboembolic complications
Kidney failure
Quality of Life

Summary of the health technology assessment:

Method and patient category

PNH is a rare hematopoietic disorder leading to intravascular hemolysis. The disease course is variable and dependent on clone size and the ability of the bone marrow to compensate by increased erythropoiesis. Many patients develop secondary bone marrow insufficiency resulting in severe anemia. Frequent secondary complications are thrombosis and kidney failure. Current treatment consists of blood transfusions and anticoagulants, if indicated. Severe cases have a substantially increased mortality. Eculizumab is a new treatment principle consisting of an antibody that prevents complement-mediated red cell lysis. The substance is approved for use in transfusion-dependent patients or patients with life-threatening PNH-induced thrombosis. Eculizumab costs approximately 350,000 euro/patient and year and Swedish Health Authorities (SKL) discourages use except in very severe cases mainly for economic reasons, but also expresses some concerns regarding documentation of efficiency. The HTA report critically assesses the evidence for patient benefit with eculizumab treatment.

Level of evidence

The literature search identified nine reports based on two large multicentre studies with altogether 195 cases. In addition, we found two short case series with Korean and Japanese patients. There was one RCT only (Hillmen 2006) and the remaining material consisted of uncontrolled open cohort data ("before-and-after") using the placebo group in the RCT as historical controls, or lacking controls ("before-and-after"). Only transfusion dependent patients were included in the studies (4 transfusions or more/12 months in the RCT and one transfusion/12 months in the largest cohort study respectively). Efficiency in non-transfusion-dependent patients has not been evaluated. Five patients participating in these studies became pregnant and this case series was described in a separate publication (Kelly 2010).

Eculizumab increased 5-year survival from 67% in historical controls (no details given) to 96% in treated patients (very low quality of evidence, GRADE ⊕). Eculizumab also reduced transfusion requirements (moderate quality of evidence, GRADE ⊕⊕⊕), thromboembolic complications (low quality of evidence, GRADE ⊕⊕) and the risk for kidney failure (very low quality of evidence, GRADE ⊕). Eculizumab ameliorated fatigue and improved QOL as measured by validated scales (low quality of evidence, GRADE ⊕⊕). Since only relative data are presented in the key publication, the clinical relevance of this effect is hard to evaluate.

Efficacy in non-transfusion dependent patients remains undocumented (very low quality of evidence, GRADE ⊕)

Reported serious adverse events were rare. Patients need to be vaccinated against meningococcal infection.

Ethical and economical aspects

The most well documented effects are a reduced need for blood transfusions and improved QOL. Treatment with eculizumab costs approximately € 350,000/patient/year. This cost is very difficult to handle for an individual clinic and SKL (Swedish Association of Local Authorities and Regions) accordingly does not recommend use of eculizumab for economic reasons. However, this decision raises ethical concerns: is it ethically reasonable to withhold an effective treatment for economic reasons only? Expressed differently: how much is improved QOL allowed to cost?

Concluding remarks

There is convincing evidence that eculizumab reduces transfusion requirements and weaker evidence that it reduces the risk for thromboembolic complications and kidney failure. Eculizumab significantly also ameliorates quality of life and reduces fatigue, but the magnitude of this effect cannot be ascertained from the studied literature. Documentation exists for transfusion-dependent patients only. Disease course varies markedly depending on clone size and the occurrence of concomitant bone marrow insufficiency, and the role of these factors for the magnitude of the therapeutic response needs to be further evaluated. Currently, SKL as well as the Swedish PNH group recommends restricted use in Sweden, the PNH group being responsible for selecting the few patients for treatment. More research is needed to identify the patient groups where the benefit of treatment motivates the exceedingly high cost.

On behalf of the Regional HTA Centre of the Western Region in Sweden

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The Regional Health Technology Assessment Centre (HTA-centrum) of Region Västra Götaland, Sweden (VGR) has the task to make statements on HTA reports carried out in VGR. The statement should summarise the question at issue, level of evidence, efficacy, risks, and economical and ethical aspects of the particular health technology that has been assessed in the report.

Bengt Sallerfors, MD, associate professor hematology, Halland Hospital Halmstad Sahlgrenska University Hospital, Göteborg, requested the present HTA. The HTA was accomplished during the period of 2010-11-03—2011-11-23. Last search updated April 2011.

A working group under the chairmanship of Bengt Sallerfors, MD, associate professor hematology, Halland Hospital Halmstad produced the HTA report. The other members of the working group were Nevzeta Kuric, MD, Dept. of Medicine, Halland Hospital Halmstad, Lena Jansson, PhD med, MSc Pharm, Dept. of Pharmacy, Halland Hospital Halmstad, Patrik Olsson, MSc Pharm, Director, Dept. of Pharmacy, Halland Hospital Halmstad, Bengt Widgren, MD PhD med, Dept. of R&D, Halland Hospital Halmstad

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