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Eculizumab treatment in paroxysmal nocturnal hemoglobinuria

B Sallerfors, T Franzén, L Jansson, N Kuric, P Olsson, P Sjögren, T Svanberg, B Widgren, H Sjövall

VÄSTRA GÖTALANDSREGIONEN
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Eculizumab treatment in paroxysmal nocturnal hemoglobinuria [Eculizumab behandling av paroxysmal nokturn hemoglobinuri]

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  Eculizumab treatment in paroxysmal nocturnal hemoglobinuria (PNH)

  Question at issue
  Does treatment with eculizumab reduce mortality, reduce the need for blood transfusions, reduce the risk for thromboembolic events and increase quality of life (QOL) in PNH patients with or without anemia, as compared to standard treatment with blood transfusions and if indicated anticoagulation?

  PICO:
  P = Patients, all ages, with classic paroxysmal nocturnal hemoglobinuria (PNH) diagnosed by immunophenotyping
  I = Eculizumab (Soliris®)
  C = Standard Treatment
  O = Mortality, Transfusion Requirements, Thromboembolic complications, Kidney failure, QOL, Complications, Side effects

- Studied benefits and risks for patients with the new health technology

  Most of the documentation consists of uncontrolled studies with a "before-and-after" design. The one exception is the RCT by Hillmen *et al*., (2006). One cohort study (Kelly *et al*., 2011), with the main outcome mortality, used a historical control material that is not described. Moreover, in both studies, transfusion-dependent patients only were included (four transfusions or more/12 months).

  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 ⊕⊕).

  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 questions

  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?

- Economical aspects
  See under ethics

Which health technology or method will be assessed?

Eculizumab treatment in paroxysmal nocturnal hemoglobinuria

1a. Who will lead the project?
Bengt Sallerfors, MD, associate professor hematology, Halland Hospital Halmstad

1b. Who posed the question?
Bengt Sallerfors

1c. Additional parties who posed the question?
Co-workers:
Nevzeta Kuric, MD, Dept. of Medicine, Halland Hospital Halmstad
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Bengt Widgren, MD, PhD med, Dept. of R&D, Halland Hospital Halmstad

1d. Other participants, from the HTA centre
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Peter Johansson, MD, PhD, NU-Hospital Organization, Uddevalla

1e. Are there any conflicts of interest for the proposer or any of the participants in the work group?
No

Disease/disorder of Interest and Present Treatment

2a. Disease/disorder of interest and its degree of severity

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired hematopoetic stem cell disorder. Mutation in the phosphatidylinositol glycan anchor biosynthesis, class A (PIG-A) gene causes deficiency or lack of glycosyl phosphatidylinositol (GPI) linked proteins, complement regulatory protein (CD59) and complement decay-accelerating factor (CD55). A lack of CD55 and CD59 leads to complement system mediated destruction of PNH erythrocytes (intravascular hemolysis). Dominant symptoms are anemia, hemoglobinuria, abdominal pain, dysphagia, thrombosis, pulmonary hypertension and impaired kidney function. The clinical presentation of the disease varies among patients related to severity of the mutation in the PIG-A gene and the mutant clone size. Spontaneous remissions do occur. Patients may have PNH without bone marrow disease, or may develop a concomitant bone marrow failure (most commonly aplastic anemia). When this happens, an increase in bone marrow activity can no longer compensate for the anemia caused by hemolysis. In patients with bone marrow failure, the disease is consequently more severe and may become life threatening. It is hard or impossible to predict actual disease course in the individual patient. Thromboembolic disease occurs in approximately half of the patients and is considered to be a common cause of death.

- ☑ a) Risk of premature death
- ☐ b) Risk of permanent illness or damage, or reduced quality of life
- ☐ c) Risk of disability and health-related quality of life

2b. Prevalence and incidence of the disease/disorder

PNH is a rare disease. Reliable incidence and prevalence data are largely lacking. According to a retrospective study, the estimated incidence in Britain is 1.3/million/year and the prevalence 15.9/million. (Hill *et al*., 2007).

In Sweden, there are about 50 known patients with PNH. (Database for rare diseases, Swedish National Board of Health and Welfare). Median age at diagnosis was 35 years, with no significant gender difference. Median survival in historical studies was 10-15 years (Hillmen *et al.*, 1995 and Socié *et al.*, 1996). In a French study from 2008, the median survival was 22 years (de Latour *et al.*, 2008).

There are probably patients with a small PNH clone and functioning bone marrow that remain undiagnosed until complications such as thrombosis or anemia occur. The availability of a potentially effective treatment might increase awareness of the disease and result in fewer undiagnosed cases.

There is an observational PNH registry (sponsored by the manufacturer of eculizumab) that includes PNH patients regardless of clone size, associated bone marrow disease, symptoms or treatment. To the date of November 2011 there are 1,100 patients registered, 22 of whom are from Sweden. The PNH registry will help to prospectively define the natural course of disease and treatment outcomes, and thereby help define treatment indications.

2c. Present treatment of the disease/disorder in the outpatient setting/ in-patient setting

Patients with anemia and/or thrombosis are usually identified in primary care. If hemolysis is evident, the patient is generally referred to a hematologist. A very small proportion of all patients with hemolysis have PNH. Diagnosis is based on flow cytometric analysis (FCA) of blood cells. Both erythrocytes and granulocytes are analyzed. In FCA, biochemical markers are used in order to identify and quantify the populations of normal and GPI-deficient cells ("relative clone size"). Bone marrow examination is also conducted. Screening for PNH in patients with thrombotic disease of unknown origin is being discussed, but is not yet implemented in routine care.

Asymptomatic patients with small PNH clones are currently not considered eligible for treatment. Patients with symptomatic anemia are generally treated with repeated blood transfusions. Patients are also substituted with iron and folic acid if indicated. In patients needing frequent transfusion, deferoxamine may be used to avoid liver damage (secondary haemochromatosis) due to iron overload. Genetically engineered erythropoietin (rhEPO) has been advocated as an alternative to repeated transfusions. Steroids and/or androgens have also been proposed to be useful in acute episodes of increased hemolysis.

Anticoagulants (warfarin and low-molecular heparin) are used to reduce the incidence of thrombosis. The only curative treatment is allogeneic bone marrow transplantation. This treatment has a significant morbidity and mortality and is used only in specific severe cases.

The Swedish Society of Hematology (SFH) has formed a PNH group with the directive to develop national guidelines for the investigation, treatment and follow-up of patients with PNH. These guidelines have recently been published (Svenska PNH-gruppen 2011).

2d. Number of patients per year who undergo current treatment regimen?

See section 2b.

2e. The normal pathway of a patient through the health care system

Patients with hemolysis and/or thrombotic disease are usually referred from primary care or from another clinic. If the anemia is mild and patients have subtle symptoms, there may be a considerable patient's and doctor's delay before the patient is referred to a hematologist. Hemoglobinuria is sometimes misinterpreted as hematuria.

2f. Actual wait time in days for medical assessment/treatment

Patients with a rapid development of anemia and hemolysis of unknown origin are referred urgently to a hematologist.

Present Health Technology

3a. Name/description of the health technology at issue

Eculizumab treatment in paroxysmal nocturnal hemoglobinuria (PNH).

3b. The work group's understanding of the potential value of the health technology

PNH is a rare disease with a heterogeneous natural course. In addition to allogeneic stem cell transplantation of a few selected patients, there is no curative treatment. Patients with symptomatic hemolysis have mostly been treated with blood transfusions and patients with thromboembolic complications with conventional anticoagulation drug therapy.

In 2007, the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMEA) recommended the granting of marketing authorization for eculizumab. Eculizumab is a humanized IgG monoclonal antibody to human factor C5. It reduces intravascular hemolysis by binding and inactivating the complement factor C5 responsible for triggering the hemolytic process. According to the EMEA Scientific Discussion document and the Summary of product Characteristics, eculizumab is indicated for treatment of patients with PNH but it is pointed out that evidence of clinical benefit of eculizumab in the treatment of patients with PNH is restricted to patients with a need for blood transfusions (EMEA, 2011). The indication can therefore be interpreted as limited to PNH patients with transfusion-demanding hemolysis.

Treatment with eculizumab is a new therapeutic option for PNH patients and is targeted at blocking hemolysis. The scientific evidence is so far limited. A reduction in hemolysis, a reduced transfusion requirement and an improved QOL have been reported. Treatment is symptomatic and knowledge about possible long-term side effects is limited.

The few studies that are published have been conducted at major national centers and primarily in transfused patients with large mutant clones. It is therefore difficult to know how applicable the results of these studies are to non-transfused patients. Experience in pregnant patients is mainly based on inadvertent pregnancies in subjects participating in eculizumab studies.

Since PNH is a rare disease, treatment with eculizumab is uncommon even in large hospitals. Most physicians in hematology will not see any, or very few, PNH patients where treatment with eculizumab may be indicated. The handling of these patients therefore probably needs to be centralized. Another aspect is that the introduction of often extremely expensive drug therapies for rare diseases is difficult to finance within standard hospital drug budgets. From this point of view it is reasonable to introduce a new structure for national assessment and funding of this type of drug treatments in order to achieve the goal of equitable health care.

3c. The central question for the current HTA project in one sentence

Does treatment with eculizumab reduce mortality, reduce the need for blood transfusions, reduce the risk for thromboembolic events and increase QOL in PNH patients with or without anemia, as compared to standard treatment with blood transfusions and if indicated anticoagulation?

3d. PICO P= Patients, I= Intervention, C= Comparison, O=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 = <u>Primary outcome:</u>
Mortality

<u>Secondary outcomes:</u>
Transfusion Requirements,
Thromboembolic complications
Kidney failure
Quality of Life

3e. Key words
paroxysmal nocturnal hemoglobinuria, pregnancy, eculizumab
paroxysmal nokturn hemoglobinuri, graviditet, eculizumab

Review of the Level of Evidence

4. Search strategy, study selection and references – appendix 3

(Search strategy, Eligibility criteria, Selection process – flow diagram, References)

During December 2010, with an update in April 2011, literature searches were performed in PubMed, EMBASE, the Cochrane Library and a number of HTA-databases. Reference lists of relevant articles were also scrutinized for additional references. A total of 376 publications were identified after removal of duplicates, of which 350 abstracts were excluded by the library. Another eight articles were excluded by the library after having been read in full text. 18 articles were sent to the work group for assessment. 11 of these articles are included in the report. Only one study was an RCT that has been critically appraised (checklists from SBU regarding randomized controlled trials). We also identified one observational cohort study with historical controls that was assessed according to checklists developed by professor Olle Nyrén, Karolinska Institute, Stockholm (Nyrén), and SBU (checklists from SBU regarding cohort studies).

Search strategies, eligibility criteria and a graphic presentation of the selection process are shown in Appendix 3. The literature search and exclusion of abstracts were done by two librarians (TS, TF), in consultation with the HTA-centre and the work group.

5a. Describe briefly the present knowledge of the health technology

The systematic literature search identified 11 studies fulfilling the PICO. The material consisted of data from three main studies: an open-label case series ('before-and-after', Hillmen *et al*., 2004, n=11), a randomized, double-blind, multicentre, placebo-controlled, prospective, phase III study (TRIUMPH, Hillmen *et al*., 2006, n=87), and an open, multicentre, prospective study (SHEPHERD, Brodsky *et al*., 2008, n=97) where placebo-treated subjects from the TRIUMPH study were used as controls regarding side effects. Most of the conclusions were however based on a 'before-and-after' design. Data from these materials were subsequently followed and reanalyzed retrospectively with new outcome variables (Appendix 4) in several additional publications. The clinical features of the cumulated patient material (Hillmen *et al.,* 2010) are summarized in Appendix 5. Data from another subgroup, consecutive patients seen during 2002-2010 in one centre (Leeds), were also presented in separate publications (e.g. Schubert *et al*., 2008; Kelly *et al*., 2011). A majority of these patients probably emanate from the TRIUMPH and SHEPHERD materials. We also identified two separate case series based on Japanese (Kanakura *et al*., 2011, n=29) and Korean patients (Kim *et al*., 2010, n=6).

Results of literature search:

It should be stressed that the inclusion criteria for two main underlying studies TRIUMPH (Hillmen *et al*., 2006) and SHEPHERD (Brodsky *et al*., 2008) differed with regard to transfusion requirements: in TRIUMPH, four transfusions or more/12 months, and in SHEPHERD one transfusion/12 months.

Only one study attempted to analyze effects on mortality (Kelly *et al*., 2011). The patient material consisted of single centre patients recruited between 2002-2010 (n=79, 34 of which participated in previous studies), as compared to traditionally treated historical controls (1997-2004, n=30). Importantly, no details regarding the control material were given. 5-year survival increased from 66.8% (CI 41.4-85.1%) in controls to 95.5% (CI 87.6-98.5%), p=0.01, in eculizumab-treated patients. The paucity of publications with this outcome in combination with serious quality issues in the one only available study motivate the assessment: very low quality of evidence (GRADE ⊕) for an effect of eculizumab on mortality.

Effects on transfusion requirements were analyzed in eight studies (Appendix 1). One study (Hillmen *et al*., 2006) was considered to be of moderate quality (based at least partially on RCT data). However, in the placebo group there were more patients with a history of aplastic anemia than in the eculizumab group (27% and 14%, respectively) (Hillmen, 2006; Hillmen *et al*., 2006; Kathula, 2006). In addition, the median duration of PNH was 9.2 years in the placebo group and 4.3 years in the eculizumab group. Both these differences may have favored the eculizumab group (Hillmen *et al*., 2006; Kathula, 2006). Although thrombosis was not an end point in the study, the use of anticoagulant agents was more frequent in the eculizumab group (49%) than in the placebo group (25%) (Hillmen, 2006; Kathula, 2006; Hillmen *et al*., 2006). The remaining studies were considered to be of low quality since they lacked controls. Eculizumab reduced the need for transfusions in the studied patient groups. Moderate quality of evidence (GRADE ⊕⊕⊕).

Thromboembolic complications were analyzed in two papers considered to be of low quality (Hillmen *et al*., 2007; Kelly *et al*., 2011). In the cumulated material (n=195), eculizumab led to a 92% relative reduction in the number of thrombotic events. In the Leeds material (n=61) eculizumab reduced the number of thrombotic events from 5.6 to 0.8 per 100 patient years (p<0.001) (Kelly *et al*., 2011). Low quality of evidence (GRADE ⊕⊕).

Incidence of kidney failure was studied in two papers (Hillmen *et al*., 2010, Kanakura *et al*., 2011). Both were considered to be of low quality. Eculizumab improved kidney function in 32% and 41% respectively, as compared to 17% with conservative treatment (p<0.001). Very low quality of evidence (GRADE ⊕).

Quality of life (QOL), was analyzed in five papers, all except one being of low quality (Hillmen *et al*., 2004; Hill *et al*., 2005; Hillmen *et al*., 2006; Brodsky *et al*., 2008; Kanakura *et al*., 2011). QOL was quantified with validated scales (FACIT-fatigue and EORTC QLC-C30 instruments). The FACIT-fatigue scale was not validated in PNH patients (Dmytrijuk *et al*., 2008). Eculizumab treatment improved both global health scores and a various subcomponents (physical functioning, emotional functioning, cognitive functioning, fatigue). Low quality of evidence (GRADE ⊕⊕).

Side effects were analyzed in most publications. Adverse events occurred in 10-50% of the patients in the SHEPHERD material (Brodsky *et al*., 2008), the majority (96%) being mild to moderate in intensity (headache, nasopharyngitis, GI problems). 44 serious adverse events occurred during the 52 week treatment, of which seven were considered possibly related to study drug (pyrexia, headache, abdominal distension, viral infection, anxiety and renal impairment).

Outcome of pregnancy in patients treated with eculizumab was analyzed in one case series (Kelly *et al*., 2010). Inadvertently, five out of 106 females participating in eculizumab studies became pregnant (pregnancy was an exclusion criterion). Mothers completing their pregnancy under eculizumab treatment bore healthy babies but the material is too small to allow any firm conclusions regarding efficacy or safety in pregnancy.

5b. Outcome tables – Appendix 1

5c. Excluded articles – Appendix 2

5d. Ongoing research

A search in Clinicaltrials.gov (2011-12-08) using the words *eculizumab OR soliris* identified 12 studies involving PNH patients. It seems that at least four of these protocols described already published studies, or parts thereof, (i.e. TRIUMPH and SHEPHERD). Except for TRIUMPH, there was one trial protocol described as an RCT (2011). This RCT protocol was on safety of eculizumab. The remaining protocols described various non-randomized studies on safety and efficacy. One protocol also described the International PNH Registry (www.pnhregistry.org), which will make it possible to continuously follow these patients.

6 Which medical societies or health authorities recommend the new health technology?

The PNH group in Sweden has published a national recommendation for the treatment of PNH (Svenska PNH-gruppen, 2011). They advocate centralization of handling of these patients, with each individual patient considered for eculizumab treatment being evaluated by the national PNH group. Relative indications listed include substantial transfusion requirement and life-threatening thrombosis.

The Swedish Association of Local Authorities and Regions (SKL) advisory committee for new drug therapies has also published recommendations regarding the use of eculizumab (NLT-gruppen, 2010). The recommendation states that eculizumab should not normally be used for the treatment of PNH at the price level currently indicated. If treatment is considered indispensable, the national recommendations for diagnosis, treatment and follow-up of patients with PNH, which has been prepared by the Swedish PNH group within the Swedish Society for Hematology, should be followed (Svenska PNH-gruppen, 2011).

☐ The National Board of Health and Welfare

☐ Medical societies

☐ Other health authority

Which medical society or health authority?

Swedish PNH Group, Swedish Society of Hematology (SFH)
The Swedish Association of Local Authorities and Regions (SKL)

Ethical aspects

7a. Ethical consequences

The fundamental ethical conflict stands between equal rights to medical treatment for all humans as opposed to risks for displacement effects due to very high costs. The exact patient population that will benefit from treatment is not well defined. On the other hand, to refrain from the treatment for purely economic reasons (as recommended by the SKL) is an ethically problematic strategy.

7b. Will other patient groups or other treatments be adversely affected (displaced) due to an introduction of the new health technology?

Yes, probably. The treatment is extremely expensive implying risks for displacement effects .

Organisation

8a. When can this new health technology be put into practice?

Already in use.

8b. Is this technology used in other hospitals in Western Region of Sweden?

Approximately 14 patients are currently treated with eculizumab in Sweden.

8c. According to the work group, will there be any consequences of the new health technology for personnel?

The treatment is given as an intravenous infusion every other week at outpatient clinics.

8d. Will there be any consequences for other clinics or supporting functions at the hospital or in the whole Western Region of Sweden?

In the County of Halland there is at present time one patient with PNH treated with eculizumab.

Economy

9a. Present costs of currently used technologies.

A blood transfusion costs about € 230. Normally the patient is given two blood transfusions at a cost of € 350. In addition, certain testing and doctor visits once a month.

9b. Expected costs of the new health technology

Treatment with eculizumab costs about € 350,000/year per patient.

9c. Total change of cost

In a blood transfusion independent patient, the total cost increase is € 350,000

9d. Can the new technology be adopted and used within the present budget (clinic budget/hospital budget)?

The additional drug costs do not fall within the clinic's budget and are not considered be accommodated within the hospital's drug budget. In a recent recommendation by SKL (2010) the Swedish counties are discouraged from funding the treatment with eculizumab for economic reasons.

9e. Are there any available analyses of health economy? Cost advantages or disadvantages?

West Midlands Health Technology Assessment Collaboration Group has published a report in 2008 including an economic analysis (Connock *et al*., 2008). The report states that there are no accurate estimates of resource costs for standard care (Connock *et al*., 2008). Therefore precise estimates of incremental cost effectiveness ratio (ICER) in terms of cost per life years gained (LYG) cannot be developed.

Unanswered Questions

10a. Important gaps in scientific knowledge?

Effect of treatment on patients with a small PNH clone, the non-transfused patients, the efficacy and risks for pregnant patients.

Long-term effects/side effects of eculizumab treatment

10b. Is there any interest in your own clinic/research group/organization to start studies/trials within the research field at issue?

The patient in Halland is included in the international PNH registry.

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 hematopoetic 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 erythropoesis. Many patients develop secondary bone marrow insuffiency 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. Ezulizumab 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 tromboembolic 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 comcomitant 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

Göteborg, Sweden, 2011-11-23
Christina Bergh, Professor, MD.
Head of Regional HTA Centre of Region Västra Götaland, Sweden.

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
The participants from the HTA centre were Henrik Sjövall, MD, Professor, HTA centr, Sahlgrenska University Hospital and Petteri Sjögren, DDS, PhD, HTA centr, Sahlgrenska University Hospital
Thomas Franzen, librarian, HTA centr, Medical Library, Sahlgrenska University Hospital, Göteborg
Therese Svanberg, librarian, HTA centr, Medical Library, Sahlgrenska University Hospital, Göteborg.
Jüri Kartus, MD, Professor, Uddevalla Hospital and Peter Johansson, MD, Uddevalla Hospital have critically appraised the report.

Utlåtande och sammanfattande bedömning från Kvalitetssäkringsgruppen

Eculizumab behandling av paroxysmal nokturn hemoglobinuri (PNH)

Frågeställning:
Kan behandling med eculizumab reducera mortaliteten, minska behovet av blodtransfusioner, reducera risken för tromboemboliska händelser och öka livskvaliteten, hos patienter med PNH, med eller utan anemi, i jämförelse med konventionell behandling med blodtransfusion och om detta är indicerat, antikoagulationsbehandling?

PICO:
P = Patienter, i alla åldrar, med klassisk paroxysmal nokturn hemoglobinuri (PNH) diagnostiserad genom immunofenotypning
I = Eculizumab (Soliris®)
C = Konventionell behandling
O = Mortalitet, Transfusionsbehov, Tromboemboliska komplikationer, Njursvikt, Livskvalitet, Komplikationer, Sidoeffekter

Resultat av HTA-processen:

Metod och målgrupp:

PNH är en sällsynt, klonal, hematopoetisk stamcells sjukdom. Uppskattad incidens i Storbritannien är 1,3/miljon/år och prevalensen är 15,9/miljon. PNH orsakas av en mutation i PIG-A genen (som kodar för fosfatidylinositolglykan klass A proteinet), vilket ger upphov till brist på GPI-ankar komplementinhibitorerna CD55 och CD59. Brist på CD55 och CD59 gör att PNH-erytrocyter utsätts för komplementsystem medierad destruktion (intravaskulär hemolys). Vanliga kliniska symtom är anemi, hemoglobinuri, buksmärtor, dysfagi, tromboser, pulmonell hypertension och njurinsufficiens. Den kliniska bilden varierar beroende på allvarlighetsgraden av PIG-A mutationen, och PNH-klonens storlek. Spontana remissioner förekommer. Patienter kan ha PNH utan benmärgssjukdom, eller utveckla benmärgssjukdom sekundärt (vanligen aplastisk anemi). När ökad benmärgsaktivitet inte längre kan kompensera för den hemolysorsakade anemin blir tillståndet allvarligare, och kan bli livshotande. Det är svårt, eller omöjligt att prognostisera sjukdomsförloppet för en individuell patient. Tromboemboliska komplikationer förekommer hos ungefär hälften av patienterna, och anses vara en vanlig dödsorsak.

Evidensläge:

Den övervägande delen av dokumentationen utgörs av okontrollerade studier med "före-efter" design. Undantaget är en randomiserad kontrollerad studie av Hillmen *et al*., (2006). En kohort studie (Kelly *et al*., 2011), med mortalitet som primärt utfallsmått, använde sig av historiska kontroller, utan närmare beskrivning av dessa. Dessutom var endast tranfusionsberoende patienter inkluderade i bägge studierna (fyra eller fler transfusioner/12 månader).
Eculizumab ökade 5-års överlevnad från 67 % hos historiska kontroller (beskrivning saknas) till 96 % hos behandlade patienter (otillräckligt vetenskapligt underlag, GRADE ⊕). Eculizumab minskade transfusionsbehovet (måttligt starkt vetenskapligt underlag, GRADE ⊕⊕⊕), minskade tromboemboliska komplikationer (begränsat vetenskapligt underlag, GRADE ⊕⊕), samt reducerade risken för njursvikt (otillräckligt vetenskapligt underlag, GRADE ⊕).
Eculizumab minskade trötthet (fatigue), och förbättrade livskvalitet, uppmätt med validerade skalor (begränsat vetenskapligt underlag, GRADE ⊕⊕).
Effekten hos patienter utan transfusionsbehov är odokumenterad (otillräckligt vetenskapligt underlag, GRADE ⊕).

Komplikationer och biverkningar:

Rapporterade allvarliga sidoeffekter var sällsynta. Patienter som behandlas med eculizumab måste vaccineras mot meningocock-infektion.

Etiska aspekter:

De mest väldokumenterade effekterna är reducerat transfusionsbehov, samt förbättrad livskvalitet. Eculizumab behandling kostar ungefär € 350 000/patient/år. Denna kostnad är mycket svår att hantera för en enskild klinik och följaktligen rekommenderas inte eculizumabanvändning av SKL (Sveriges Kommuner och Landsting), av ekonomiska skäl. Detta beslut väcker, hur som helst, etiska frågor: Är det etiskt försvarbart att undanhålla en effektiv behandling av endast ekonomiska skäl? Eller annorlunda uttryckt: Hur mycket får förbättrad livskvalitet kosta?

Ekonomiska aspekter: Se under Etiska aspekter

För HTA-kvalitetssäkringsgruppen
Göteborg, Sverige, 2011-11-23
Christina Bergh, Professor

HTA-kvalitetssäkringsgruppen har ett uppdrag att yttra sig över genomförda HTA i Västra Götalandsregionen. Yttrandet skall innefatta sammanfattning av frågeställning, samlat evidensläge, patientnytta, risker samt ekonomiska och etiska aspekter för den studerande teknologin.

Denna HTA har genomförts på begäran av Bengt Sallerfors, verksamhetsområdeschef, docent, Akut- och medicinkliniken, Länssjukhuset i Halmstad
Från HTA-centrum har Henrik Sjövall, professor (huvudansvarig) och Petteri Sjögren varit resurspersoner tillsammans med Thomas Franzén, bibliotekschef, samt Therese Svanberg, HTA-bibliotekarie, båda SU/Sahlgrenska sjukhuset. HTA-rapporten och åberopad och förtecknad litteratur har sedan granskats av Jüri Kartus, professor, överläkare, FoU-chef NU-sjukvården samt Peter Johansson, överläkare, hematolog, verksamhetsområde specialistmedicin, NU-sjukvården.

Slutsatser har diskuterats vid möten mellan HTA-centrum och HTA-projektgruppen. Ett utlåtande har tagits fram, diskuterats och fastställts vid HTA-kvalitetssäkrings-gruppens möte 2011-11-23 Projektet har pågått under perioden 2010-11-03 –2011-11-23.Sista uppdatering av artikelsökning var april 2011.

HTA-kvalitetssäkringsgruppen:

Christina Bergh	Anders Larsson	Maria Skogby
Professor, överläkare	Överläkare	Med dr, vårdenhetschef
Thomas Franzén	Christian Rylander	Annika Strandell
Bibliotekschef	Med dr, överläkare	Docent, överläkare
Magnus Hakeberg,	Ola Samuelson,	Therese Svanberg
Professor, övertandläkare	Docent, överläkare	HTA-bibliotekarie
Lennart Jivegård,	Petteri Sjögren	Kjell-Arne Ung
Docent, universitetslektor	Med dr, tandläkare	Docent, överläkare
Peter Johansson	Henrik Sjövall	Margareta Warrén Stomberg
Med dr, överläkare	Professor, överläkare	Docent, överläkare

Appendix 1

Outcome variable: Mortality

Author, year Country	Study design	Result Intervention - Control	Comments	Quality (may vary according to outcome)
Kelly R., 2011, UK	Retrospective case series (consecutive patients in Leeds 2002-2010, n=79) compared with traditionally treated historical controls (1997-2004, n=30)	5 year survival: Controls 66.8% (CI 41.4-85.1%). Eculizumab-treated patients: 95.5% (CI 87.6-98.5%), p=0.01.	Historical control material that is not described. Patients included also in other studies?	**Very low**

Appendix 1

Outcome variable: Transfusion requirements

Author, year Country	Study design	Result Intervention - Control	Comments	Quality (may vary according to outcome)
Brodsky R.A., 2008, UK	Open-label phase III multicenter study with controls from placebo-treated TRIUMPH material, n=97 included, 1 dropout	Mean 12.3 units/patient/year, before treatment, and 5.9 units/patient/year, after treatment (p<0.001). Median 8.0 units/patient/year, before treatment, and 0.0 units/patient/year, after treatment (p<0.001).		**low**
Hill A., 2005, UK	Open-label case series, extension study to Hillmen *et al*., 2004 ("before-and-after design"), n=11, no dropouts	Mean 2.1 units/patient/month before treatment, and 0.5 units/patient/month, 64 weeks after treatment (p=0.001). Median 1.8 units/patient/month before treatment, and 0.3 units/patient/month, 64 weeks after treatment (p=0.001).		**low**
Hillmen P., 2004, UK	Open-label case series ('before-and-after design'), n=11, no dropouts	Mean 2.1 units/patient/month, 12 months before eculizumab treatment, and 0.6 units/patient/month, after 3 months of treatment. Median 1.8 units/patient/month, 12 months before eculizumab treatment, and 0.0 units/patient/month, after 3 months of treatment (p=0.003).		**low**
Hillmen P., 2006, UK	Double-blind randomized placebo controlled multicenter phase III trial, n=87, dropouts: 2	Median 10 units/patient/6 months resp. 0 units patient/6 months during treatment (p<0.001)	Median duration of PNH in control group 9.2 mo, in eculizumab group 4.3 mo. 12 % aplastic anemia in control group, 6% in eculizumab group (n.s.)	**moderate**

Appendix 1

Outcome variable: Transfusion requirements

Author, year Country	Study design	Result Intervention - Control	Comments	Quality (may vary according to outcome)
Schubert J., 2008, UK	Retrospective analysis of patients from double-blind randomized placebo controlled multicenter phase III trial (TRIUMPH) + from open-label multinational phase III trial (SHEPHERD), n=87+97, not defined	TRIUMPH: placebo: 10 units/26 weeks, eculizumab: 0 units/26 weeks; SHEPHERD: 8 units/1 year; eculizumab: 0 units/1 year		**low**
Kanakura Y., 2011, Japan	Case series/open-label phase II cohort study, n=29, 2 dropouts	Mean 5.2 units/12 weeks at baseline, 1.5 units/12 weeks after 12 weeks (p=0.006)	Japanese patients	**low**
Kelly R., 2011, UK	Open retrospective case series (‘before-and-after’), n=61, dropouts not relevant. Consecutive patient in Leeds 2002-2010.	Mean 19.3 transfusions/year before treatment, 5.0/year after treatment (p<0.001)	Patients included also in other studies?	**low**
Kim J.S., 2010, Korea	Case series (‘before-and-after’), n=6	Median before eculizumab: 1.5 (0-12) units/3 months; after eculizumab: 0 (0-6) units/3 months, p=not stated		**low**

Appendix 1

Outcome variable: Thromboembolism

Author, year Country	Study design	Result Intervention - Control	Comments	Quality (may vary according to outcome)
Hillmen P., 2007, UK	Retrospective analysis of open-label multinational phase III trial, RCT (TRIUMPH) + extension studies; n=195 (11+87+97)	Thrombotic events (TE) as measured by ultrasound, CT, MR, angiograms. Number of TE reduced from 39 to 3 (relative reduction 92%). In patients receiving antithrombotics: 10.6/100 patient years; eculizumab: 0.62 events/100 patient years ($p<0.001$).		**low**
Kelly R., 2011, UK	Open retrospective case series ("before-and-after"), n=61, dropouts not relevant. Consecutive patient in Leeds 2002-2010.	5.6 thrombotic events per 100 patient years before treatment, 0.8 events per 100 patient years after treatment ($p<0.001$)		**low**

Appendix 1

Outcome variable: Renal failure

Author, year Country	Study design	Result Intervention - Control	Comments	Quality (may vary according to outcome)
Hillmen P., 2010, UK	Retrospective analysis of open prospective pilot phase II study (n=11), double-blind randomized placebo controlled prospective multicenter phase III trial (TRIUMPH), n=87 + open-label multinational prospective phase III trial (SHEPHERD), n=97, total n=195.	TRIUMPH: significant improvement of chronic kidney disease stage: placebo: 17% improvement; eculizumab: 29% improvement ($p<0.005$). All studies: 32%, 8% worsened after eculizumab ($p<0.001$)		**low**
Kanakura Y., 2011, Japan	Case series/open-label phase II cohort study ('before-and-after'), n= 29, 2 dropouts	41% improved, 55% no change, 3% worsened after eculizumab ($p<0.001$)	Japanese patients only	**low**

Appendix 1

Outcome variable: Quality of life

Author, year Country	Study design	Result Intervention - Control	Comments	Quality (may vary according to outcome)
Hillmen P., 2004, UK	Open-label pilot study, n=11, no dropouts. QOL with EORTC QLC-C30 instrument	Initial global health status from 56.1 to 69.8 ($p<0.02$). 20-30% improved scores for physical functioning, emotional functioning, cognitive functioning, fatigue, dyspnea and insomnia.		**low**
Hill A., 2005, UK	Open-label extension study, n=11, no dropouts. QOL with EORTC QLC-C30 instrument	Global health status from 56.1 to 69.9 ($p<0.009$). 20-30% improved scores for physical functioning, emotional functioning, cognitive functioning, fatigue, dyspnea and insomnia, pain and constipation.		**low**
Hillmen P., 2006, UK	Double-blind randomized placebo controlled multicenter phase III trial, QOL with FACIT-fatigue and EORTC QLC-C30 instruments. n=87, 2 dropouts	Improved fatigue scores (placebo: -4.0+-1.7; eculizumab: +6.4+-1.2 points, $p<0.001$). Global health: placebo -8.5; eculizumab: +10.9, $p<0.001$; significant relative improvement in several functioning scales and symptom scales. Magnitude of effect hard to evaluate since base line values are not presented.		**moderate**
Brodsky A., 2008, UK	Open-label phase 3 multicenter study, placebo group from Hillmen *et al*., 2006 used as controls. QOL with FACIT-fatigue and EORTC QLC-C30 instruments. 107 screened (97 included), 1 dropout.	Global health score: +19.7; improvement in several functioning scales and symptom scales ($p<0.001$)	FACIT-fatique not validated in PNH patients*	**low**
Kanakura Y., 2011, Japan	Open-label phase II case series, QOL with FACIT-fatigue and EORTC QLC-C30 instruments. n=29, 2 dropouts	38% 'clinically meaningful improvement' in fatigue scores Improved QOL ($p=0.02$) with significant improvement of role- , physical- and emotional functioning. 50% improved at least 10% in global health status.	Japanese patients	**low**

* Dmytrijuk *et al*,. 2008

Appendix 2

Study (author, publication year)	Reason for exclusion
Connock, 2008	partially systematic review + opinion
Helley, 2010	wrong outcome (not clearly stated)
Hill 2010a,	wrong outcome, role antiglobulin test
Hill 2010b,	wrong outcome (dyspnoea)
Hill 2005b,	case report, 2 cases, wrong outcome
NHSC, 2006	opinion (horizontal scanning)
Risitano, 2009	wrong outcome (treatment effects related to C3 binding)

Appendix 3, Search strategy, study selection and references

Question(s) at issue:
Is treatment with eculizumab in PNH patients better than standard treatment with blood transfusions and if indicated anticoagulation?

PICO:

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

Search strategies

PubMed 2010-11-10
eculizumab OR soliris

138 results

EMBASE (OVID SP) 2010-11-10
eculizumab.mp. OR exp ECULIZUMAB/ OR (eculizumab or soliris).ti,ab,tn.
AND
(PNH OR paroxysmal nocturnal hemoglobinuria OR paroxysmal nocturnal haemoglobinuria).ti,ab. OR paroxysmal nocturnal hemoglobinuria.mp. OR exp paroxysmal nocturnal hemoglobinuria/

273 results

The Cochrane Library 2010-11-11
eculizumab OR soliris

25 results
Cochrane reviews 2
Other reviews 1
Clinical trials 18
Technology Assessments 3
Economic evaluations 3

CRD 2010-11-10
eculizumab OR soliris

5 results

SBU, Kunnskapssenteret, Sundhedsstyrelsen 2010-12-22
Nothing relevant to the question at issue was found

All searches were updated on 2011-04-21
55 results

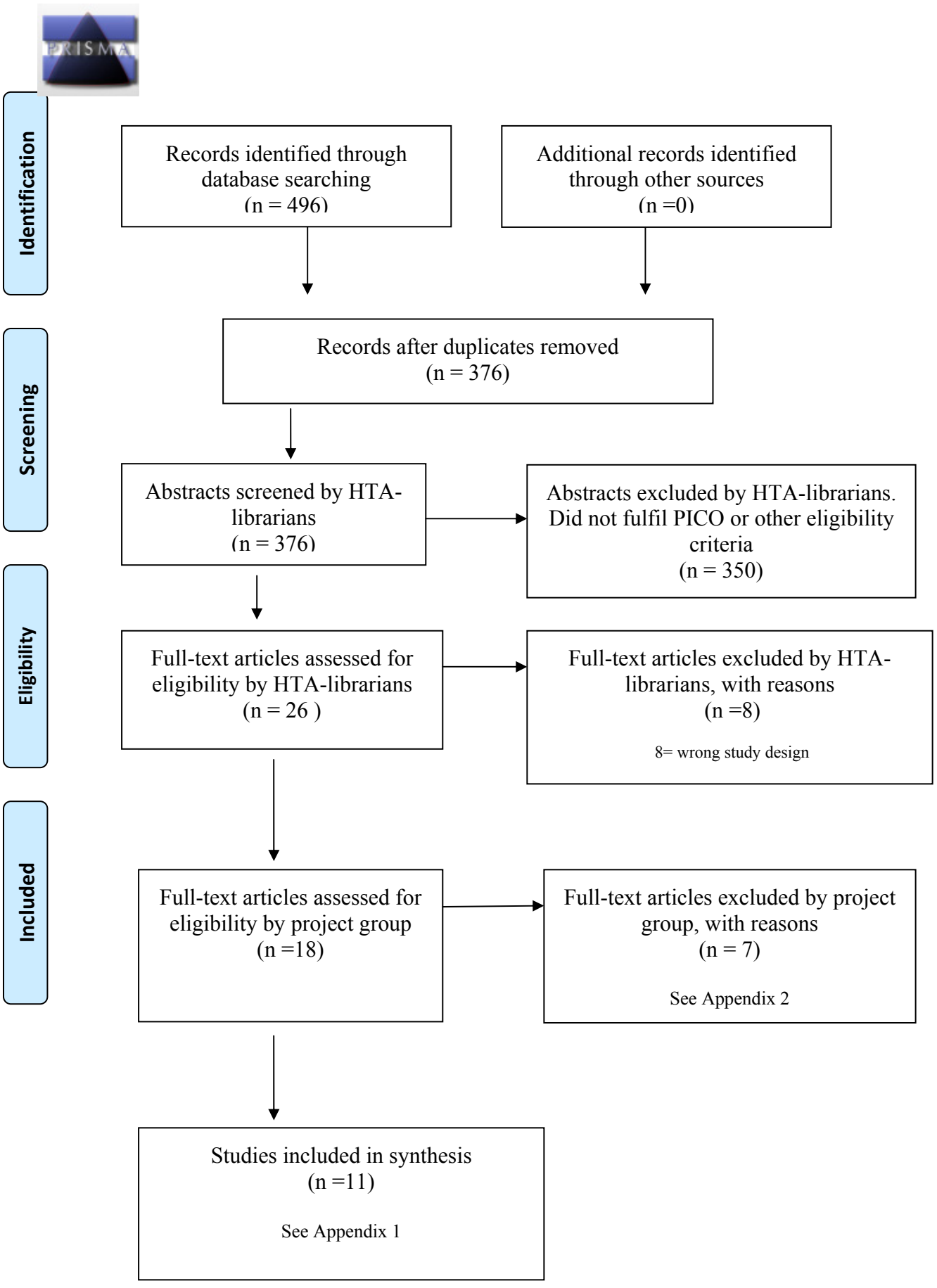
Reference lists
No additional references were identified

Eligibility criteria

Study design:
Studies with some kind of control group
Case series
No case reports with only one patient, no review articles

Language: English, Swedish, Norwegian, Danish

Selection process – flow diagram



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Excluded studies:

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Appendix 4
List of studied outcome variables

Name	Brodsky	Hill 2005a	Hillmen 2010	Hillmen 2004	Hillmen 2007	Hillmen 2006	Kelly 2010	Risitano	Schubert	Kankura	Kelly 2011	Kim
adverse events	1				1	1	1			1	1	1
mortality											1	
hemolysis (LDH AUC etc)	1	1			1	1	1	1		1	1	1
Pro-BNP												
Dyspnea												
QOL	1	1			1	1				1		
Fatigue	1								1	1		1
pharmakokinetics		1			1					1		
thrombosis					1						1	1
Transfusion requirements	1	1		1		1			1	1	1	1
Hemoglobin levels	1				1	1			1	1		1
Coagulation related laboratory parameters					1							1
antiglobulins												
dystonia symptoms												
renal function			1							1		
pregnancy outcomes							1					

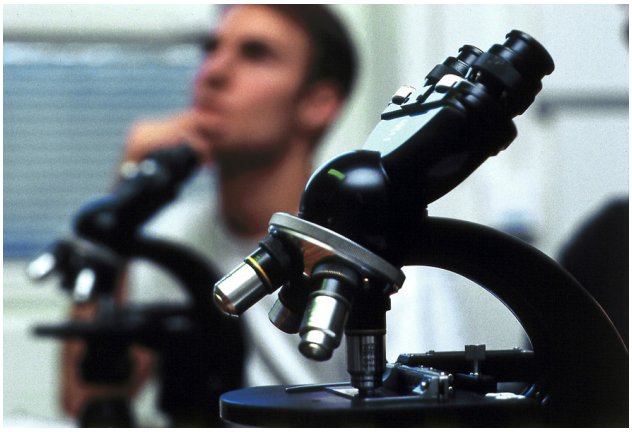
Appendix 5
Clinical data of cumulated patient material included in studies

Description	**n**	**%**	**min**	**max**
Gender, male	89	45,6		
History of AA or MDS	59	30,3		
History of previous trombosis	62	31,8		
Use of cyclosporine	13	6,6		
Use of NSAID	17	8,7		
Age (yr)	39		18	85
	median		**min**	**max**
Disease duration (yr)	5,5		0,12	38,5
PNH type III RBC proportaions (%)	32,3		2,4	98,8
Reticulocyte counts ($x10^{12}$/l)	0,164		0,036	0,757
Lactate dehydrogenase level (U7l)	2139		499	10300
Platelet count ($x10^{9}$/l)	149		23	547
n=195				

Summary of Findings: Ecuzumalib

Outcome variable Number of studies	Design	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Relative effect (95%CI)	Absolute effect	Quality of evidence GRADE
Mortality										
1	Non-randomized controlled study	Very serious limitations (-2)	Not relevant	Serious indirectness (-1)	No imprecision	Unlikely	Not relevant			⊕ Very low
Transfusion requirement										
3	1 RCT 2 non-randomized controlled studies	Some limitations (?)	Not relevant	Some indirectness (?)	No imprecision	Unlikely	Not relevant			⊕⊕⊕ * Moderate
Thromboembolic events										
2	2 non-randomized controlled studies	Serious limitations (-1)	No inconsistency	No indirectness	No imprecision	Unlikely	Large (+1)			⊕⊕ Low
Kidney failure										
1	Non-randomized controlled study	Serious limitations (-1)	No inconsistency	No indirectness	No imprecision	Unlikely				⊕ Very low
Quality of life										
1	RCT	Serious limitations (-1)	Not relevant	Some indirectness (?)	Some imprecision (?)	Unlikely	Not relevant			⊕⊕ * Low

* GRADE based on RCT only



HTA

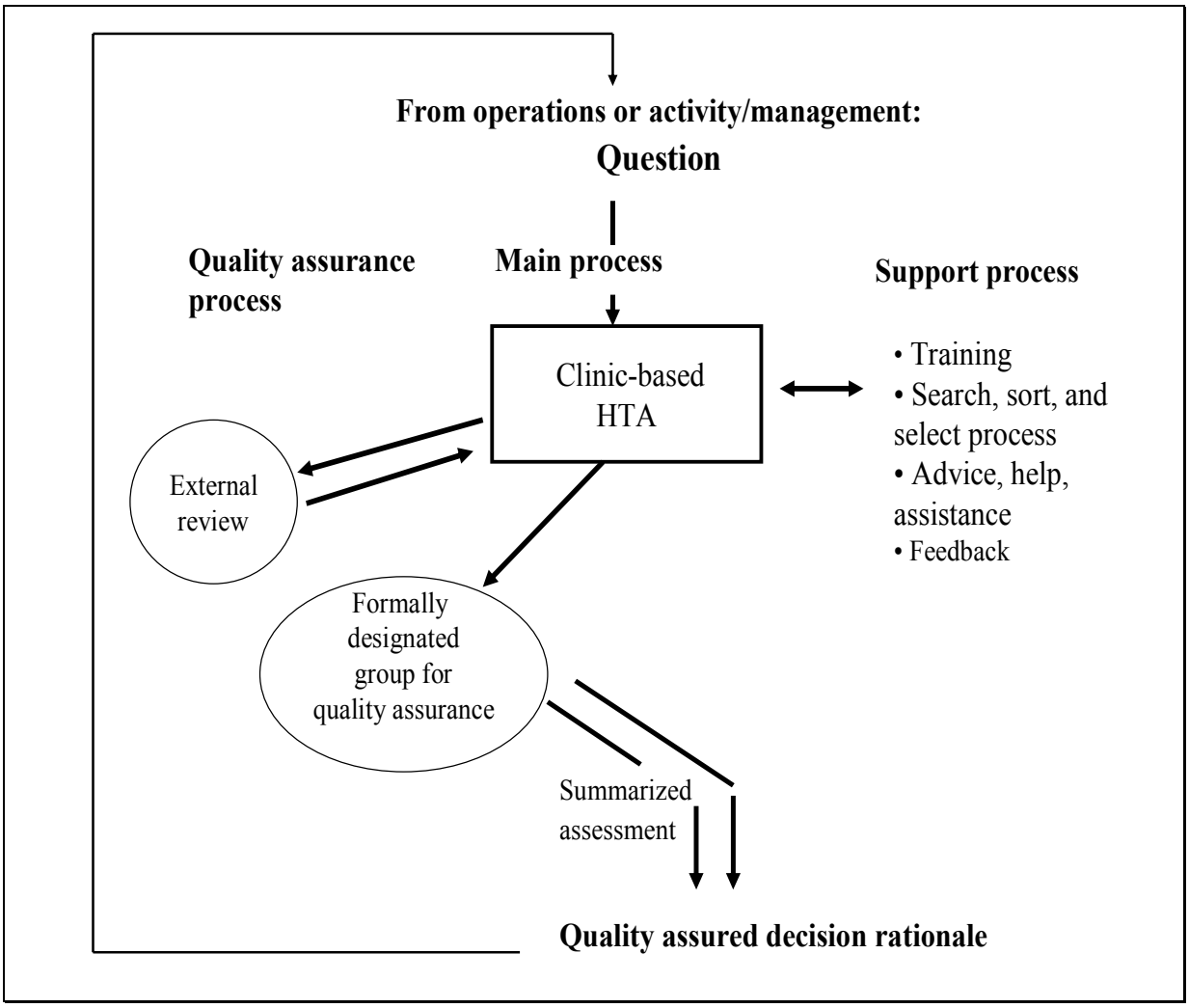
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= ⊕⊕⊕⊕
Moderate quality of evidence	= ⊕⊕⊕
Low quality of evidence	= ⊕⊕
Very low quality of evidence	= ⊕

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centre


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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