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HTA-Report | Summary

Efficacy and effectiveness of recombinant human activated protein C in severe sepsis of adults

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Health political background

Sepsis is defined as an invasion of microorganisms and / or toxins into the blood associated the reaction of the organism towards this invasion. Sepsis has a major budget impact on the intensive care unit. The drug Xigris® (= activated protein C, recombinant activated protein C, rhAPC, DAA) is a new intervention whose clinical efficacy and cost effectiveness is to be researched in this Health Technology Assessment. Selecting only patients with severe sepsis 44000 to 95000 cases can be identified with a suggested mortality of 30 to 50 % resulting into 30000 deaths per year for Germany alone. In an extrapolation for the United States, 751000 cases of severe sepsis were described per year. The incidence rises with the age from 0.2 per 1000 in infants up to 2.2 per 1000 in patients older 85 years of age. Incidence as well as case fatality was lower in females compared to males, although differences could be explained by a different profile of concurrent diseases and by differences in infection site. Between 1979 and 2000 the spectrum of causative agents changed from predominantly gram negative (1979 to 1987) to predominantly gram positive bacterias (from 1987 onwards). In Germany prevalence data for severe sepsis in intensive care units were assessed in the context of the German Prevalence study (Competencenetwork Germany SepNet). A total of 454 intensive care units in 310 hospitals were included in this study. The prevalence of sepsis was 35 % in intensive care units in Germany. Of all screened patients, 12 % had severe, and 11 % either severe sepsis or septic shock.

Scientific background

Severe sepsis is a systemic inflammatory reaction (systemic inflammatory response syndrome, SIRS), associated with acute dysfunction or failure of one or more organ systems. Failure of organ systems such as the renal or the cardiovascular system may be the consequence of a pathophysiological overreaction of the body to the infection. The clinical outcome depends on both the aggressiveness of the underlying infectious agent as well as on the immune system of the patient and its reaction to the agent. There are three categories for the severity of sepsis: sepsis with proven or assumed infection, severe sepsis with organ dysfunction and septic shock with circulatory failure. In 1992 the Consensus Conference of the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) recommended the use of standardised definitions for sepsis. Apart from the prevalence of multiorgan failure, the Acute Physiology and Chronic Health Evaluation (APACHE) II Score is used to define the severity of sepsis. The APACHE-II-Score ranges from 0 to 71 and is based on the combination of twelve routinely assessed physiological parameters, age and the original health status. An increased APACHE-II-Score is associated with higher mortality. Apart from the APACHE-II-Score the Sequential Organ Failure Assessment (SOFA) Score can be used for

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the classification of disease severity. Both the APACHE-II-Score and the SOFA-Score are, however, not validated for individual risk prediction.

In severe sepsis, the intrusion of infectious agents and the resulting host inflammatory reaction activate the coagulation system. This activation induces tissue factor-mediated thrombin generation, reduces anticoagulant mechanisms, and inhibits fibrinolysis via endothelial cells. According to the guidelines S2 of the German Society of Sepsis and the German Interdisciplinary Association for Intensive and Emergency Medicine the surgical evacuation of foci of infection plays a major role in the therapy of severe sepsis. Foci of infection include abscesses and empyemas. In addition, adequate antibiotic therapy should be started as soon as possible. Antibiotic therapy should be checked regularly and adapted accordingly. Apart from treating the underlying infection, standard supportive care should be provided. A number of drugs have investigated in phase III trials aiming to improve outcome via the modulation of the septic coagulation cascade. The role of heparin in the treatment of severe sepsis, both with and without these newer anticoagulant therapies, remains unclear. Of the newer anticoagulant agents, activated protein C has emerged as a new treatment option. The PROWESS-study, a randomised controlled phase III trial, compared activated Protein C with placebo in patients with severe sepsis. Mortality after 28 days was significantly reduced in patients receiving activated Protein C. However, in the PROWESS-study, a non-significant increase in bleeding rates was observed in the treatment compared to the control group. This increase in bleeding events occurred mainly in patients with predisposing diseases and during the infusin period.

Research questions

From the medical perspective two research questions arise. First what is the medical efficacy of DAA in the treatment of the severe sepsis in adult patients with high risk of death overall and in different subgroups. Secondly what is the medical efficacy of DAA in the treatment of the severe sepsis in adult patients with low risk of death. Health economical questions are concerning the cost effectiveness of drotrecogin alfa (activated) in the treatment of the severe sepsis versus placebo. Of what influence is the use of the APACHE-II-Score and the diffentiation of multiorgan dysfunction for the cost efficiency of DAA in the treatment of the severe sepsis. Do bleedings bring down the cost effectiveness of the new intervention. Of what impact are differences in the study cohorts and in real world use. Are the findings in other countries transferable to a German medical care context, what adjustments can be used to assure the fit.

Methods

Only trials with adults were included into this assessment. Besides this confinement no other limitations concerning the target population were used. In addition to the literature search of the DIMDI on the topic "drotrecogin alfa activated in the treatment of severe sepsis in adults" the authors have undertaken additional research in Cochrane databases. The hits have been audited on their relevance for the topic of this assessment. From this search further publications have been chosen from their abstract and / or title. The abstracts were screened systematically. Publications in other languages than German or English were excluded as well as publications focusing on other interventions and case reports. Checklists have been used for the exclusions.

Results

Medical part

The systematic literature search has yielded a total of 847 publications with regard to activated Protein C. Out of these, 165 publications were considered relevant from the medical perspective and were chosen for further investigation in full text documents. Three other relevant publications were extracted from references. Based on the research, 36 publications were included and 132 publications excluded. The included publications consisted of one HTA, of one guidance, three randomised controlled trials (RCT), and eleven phase IV trials / compassionate use studies. As they reported only the results of two of the three RCT, seven systematic reviews were excluded.

The HTA report published in 2005 and the NICE Guidance published in 2004 summarized the evidence with regard to DAA in patients with severe sepsis. In the HTA by Green et al.[2] the authors considered therapy with DAA to be effective in comparison to placebo. With regard to the subgroup analyses performed, therapy with DAA was deemed effected in the subgroup of patients with multiorgan failure (≥ 2). The authors assumed therapy with DAA to be effective not only during the initial 28 days of the PROWESS trial but also after three months. This assumption was apparently based on data provided to NICE by the manufacturer, Eli Lilly. However, in a publication by Angus et al.[1] (2004) based on the retrospective long-term follow-up of the PROWESS study, there were no significant differences in mortality between the intervention group and the control group after three months and at subsequent follow-up assessments. The authors of the HTA discussed the numerous subgroup analyses of the PROWESS study performed both prospectively and retrospectively. As adverse events of the PROWESS study, the authors described a non-significantly increased incidence of bleeding events in the intervention group. In addition, the authors summarized open research questions with regard to DAA. Similar conclusions to those of the HTA were reached in the NICE guidance.

The two RCT with regard to the primary endpoint of 28-day mortality in patients with severe sepsis showed inconsistent results. The PROWESS study showed a significant reduction in 28-day mortality with DAA compared to placebo in patients with severe sepsis and a mixed risk of death (25 % vs. 34 %; relative risk reduction 19.4 %, 95 % CI 6.6-30.5 %; absolute risk reduction 6.1 %). The ADDRESS study showed no significant difference in the 28-day mortality with DAA in comparison to placebo in patients with severe sepsis and low risk of death (18.5 % vs. 17.0 %; relative risk 1.08, 95 % CI 0.92 to 1.28). In the retrospective follow-up assessment of the PROWESS study, no differences in mortality were observed after three, six, twelve months and 2.5 years, respectively.

In the subgroup analyses of the PROWESS study, a significant reduction in mortality associated with DAA therapy was observed in the following subgroups: $< / \geq 65$ years of age, ≥ 75 years, men, caucasian, region USA / Canada, no congestive heart failure, cancer, COPD, no prior surgery, lung as infection site and / community acquired pneumonia, gram positive bacteria, DIC, protein C deficiency, prothrombin time > 14.5 to 100 s, partial thromboplastin time > 37-74 s, platelets < 140000 / µl, IL 6 ≥ 1000 pg/ml, mechanical ventilation, vasopressor support, high APACHE II (≥ 25) and high SOFA-Score (> 11), as well as multiorgan failure (≥ 2 organ systems). In the following subgroups no significant reduction in mortality was observed: women, non-caucasian, region Europe / other, congestive heart failure, no cancer, no COPD, prior surgery, abdomen, urinary tract / other as infection

site, gram negative bacteria or no microorganism, no DIC, no protein C deficiency, prothrombin time $\leq$ 14.5 s, partial thromboplastin time $\leq$ 37 s and 74 to 100 s, platelets $\geq$ 140000 / µl, IL 6 < 1000 pg / mL, no mechanical ventilation, no vasopressor support, low APACHE II (< 25) and SOFA-Score (< 11).

Serious bleeding events were the most relevant adverse events under therapy with DAA. Whereas the PROWESS study did not show any difference in serious bleeding events between intervention and placebo groups (3.5 % vs. 2.0 %; P = 0.06), the ADDRESS study showed a significantly increased bleeding rate in patients treated with DAA compared to placebo (3.9 % vs. 2.2 %; P = 0.01). The increased risk of bleeding associated with DAA led to the early stop of the ADDRESS study, as well as the lack of survival benefit in the treatment group. In most open-label and compassionate use studies, a higher mortality was observed compared to the PROWESS study. In addition, bleeding rates were increased in studies in the usual care setting compared to clinical trials. The risk of bleeding increased with decreasing level of controlled trial design (clinical trials, open-label studies, compassionate use studies). The ENHANCE study as the largest open-label, single arm trial reported a bleeding rate twice as high in the intervention group compared to the PROWESS data (6.5 % vs. 3.5 %, respectively).

Economic part

The therapy regimen of rhAPC did not lead to an increased resource use except the drug cost in the trial of Angus and colleagues. Focussing on the outcome at day 28 rhAPC costs 160000 USD per life saved. In a reference case 48800 USD per QALY were calculated. These findings are limited because their source is the PROWESS trial alone. The transfer of the observed effects is in so far restricted. Betancourt et al. show that a strict limitation to a greater number or dysfunctional organs leads to a better mortality outcome, more saved lives at lower costs. Even the bleeding events do not change this result. The recommended restriction on multiorgandysfunction corresponds to the approval in Europe. The ICER per patient was assumed to be 78075 USD per saved life. In this trial bleedings were taken into account, but the implications cannot be satisfying. Davies et al. have calculated QALY on the basis of direct costs from the perspective of the NHS. In addition to the PROWESS data British costs and EVBI results were included. The patient cohort contained only cases of multiorgan dysfunction and severe sepsis. The PROWESS trial developed costs per QALY of 6679 GBP and the EVBI of 11051 GBP. These results stay well under the threshold of 30000 GBP. Nonetheless did high LOS occur in the British context, which may lead to the conjecture of an artificial environment of the PROWESS trial and probable transfer problems of the findings. Bleedings were not reported in this trial. Fowler et al. use a decision analysis model to compute cost efficiencies. A reference case is modelled for the economy. Bleedings in form of gastro-intestinal bleedings were included as a placeholder for all early intricacies. The probabilities were taken from the PROWESS trial. Restricting the therapy to those with an APACHE-II-Score above or equal 25 the average cost per QALY ranged 13493 USD and the total cost at 57659 USD.

The HTA by Green at al.[2] enclosed three health economic studies as well as eight abstracts. Findings from the United States and Canada provide costs per life year saved of 15801 to 33000 USD and costs per QALY of 20047 to 48800 USD. Green et al.[2] defer on a greater transparency of the outcomes by Angus and Manns with respect to the presentation of the research

methods than Fowler et al. who deliver the "better" QALY. The cost effectiveness in European studies is higher than in Canada or the US because of the limitation to multiorgan dysfunction. This constraint narrows the cohort to the more severe patients with a higher mortality benefit from rhAPC.

The findings of a second study by Green et al.[2] recommend the usage of rhAPC for Great Britain. Better cost effectivenesses were calculated than for the US or Canada in this study.

Hjelmgren at al. use a markov model to identify the cost effectiveness of rhAPC for the Swedish health care system. Based on the PROWESS model alterations were performed to fit to the population in question. Trial data was connected to Swedish prices and resulted in a cost effectiveness of 21556 Euro per life year saved or 31241 Euro per QALY. Only taking those patients into account with more than two dysfunctional organs the corresponding values were 15965 Euro per LYG and 23138 Euro per QALY.

For a recommendation for the usage of rhAPC in Canada Manns et al. calculate cost efficiencies. The direct costs per saved life year differ from 25991 to 32393 USD within the age groups. Noticeable is the relevant difference depending on the severeness of the disease. Neilson et al. estimate the cost efficiencies for Germany at 14119 Euro undiscounted and at a discount rate of 3 % of 17723 Euro per life year saved. Restricting on the severe cases leads to 10215 EURO and 12880 EURO respectively (MOV). The adverse effect of bleedings is only mentioned in the summary of the study. The data is mainly extracted from the PROWESS trial, adjustments had been made for the German health care system. Riou Franca et al. analyse the cost and outcome situation in a french hospital setting. An ICER based on PROWESS data for the whole population of 19686 USD per QALY is their result.

Discussion

The PROWESS trial showed a significant reduction in 28-day-mortality associated with the use of DAA in comparison to placebo in patients with severe sepsis and a mixed risk of death. The ADDRESS trial did not show a significant reduction in mortality but showed an increased risk of bleeding associated with DAA. In the ENHANCE study, a phase-IV-study, a bleeding rate twice as high as the bleeding rate in PROWESS study was observed.

In PROWESS study, numerous subgroup analyses were performed. A significant survival benefit associated with DAA was reported for 23 subgroups, and no survival benefit for 27 subgroups. A significant treatment benefit seemed to be associated with an increased disease severity. Some of the subgroups were prospectively defined, others retrospectively. In general, subgroup analyses lead to a number of methodological problems and should only be used as hypothesis generating.

The major adverse events observed during therapy with DAA were serious bleeding events. In most open-label and compassionate use studies, the risk of bleeding was significantly higher than in the PROWESS trial. Overall, the risk of bleeding seemed to be inversely related to controlled study design. Also, the risk of bleeding was associated with prior surgery and / or the presence of coagulopathy. Prospective evaluations of long-term morbidity induced by serious bleeding events are required. Also, interventions needed to stop bleeding need to be assessed. In the retrospective long-term follow-up of the PROWESS trial, no significant differences in mortality were found between intervention- and control group. Prospectively planned studies with sufficient long-term follow-up assessments and with „intention-to-treat" analysis are needed. As organ systems may be permanently damaged in

some patients, an expert panel recommended a follow-up period of at least three to six months. In addition, other endpoints have not been determined sufficiently, such as functional ability, health-related quality of life, and morbidity following severe sepsis.

The study population of the PROWESS study was heterogeneous, as common in severe sepsis. Comorbidity and concurrent medication may influence coagulation status as well as overall mortality risk and need to be taken into account when assessing the efficacy of DAA. The role of concurrent use of heparin and/or other anticoagulants in the treatment of severe sepsis remains unclear. The relative risk reduction associated with DAA was only significant in patients without heparin therapy (25 %).

The prognosis after a period of severe sepsis differs considerably between different countries, e.g. the hospital mortality in England / Wales was approximately twice as high as in the US. Concentrating on the whole potentially to be treated group the cost efficiencies range on to top level of accepted interventions by the third party payers. Narrowing the population down to the fraction with a high lethality (MOV or APACHE-II-Score $\geq$ 25) the trials at hand report that the therapy is cost efficient. The calculated cost efficiencies then lie well below generally accepted thresholds. A treatment of all possible septic patients would have shifted the cost effectiveness into an unacceptable range. The relevant adverse event of bleedings has not been dealt with in all studies. Only three studies have reported at least the fact that bleedings occur. Calculating them into costs was often not considered. A real adjustment of the cost effectiveness might have altered the cost effectiveness in an unwished way.

Conclusions / Recommendations

To conclude, therapy with DAA seems to be associated with a significant reduction in 28-day mortality compared to placebo in patients with severe sepsis and a high risk of death. No significant survival benefit was observed in patients with severe sepsis and a low risk of death. The study assessing the effectiveness of DAA in patients with low risk of death was stopped earlier as there was an increased risk of bleeding in the treatment group. In the usual care setting, both mortality and bleeding rates were increased in comparison to the clinical trial setting. Also, the role of concurrent heparin and other anticoagulants remains unclear.

Further research is required with regard to the following issues: long-term effect of DAA on mortality, morbidity, health-related quality of life, and resource use. In addition, effectiveness of DAA in the treatment of severe sepsis needs to be determined in studies with adequate sample size for those subgroups with a lack of survival benefit. Also, studies should stratify according to any underlying disease. Alternative designs, for example studies with multiple arms comparing DAA with heparin alone or in combination, are needed, as well as studies by different research

References

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