NOTAT

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Oversigt over projekter som har modtaget tilskud fra Regionernes Medicin- og behandlingspulje 2021

Regionerne har etableret en fælles Medicin- og behandlingspulje, som bl.a. skal sikre en mere præcis anvendelse af medicin til gavn for patienter og samfundsøkonomien.

Nedenfor gennemgås de 11 projekter, som styregruppen for Regionernes Medicin- og behandlingspulje har valgt at tildele økonomisk støtte i 2021. Der henvises til puljens kommissorium om, hvilke projekter der kan opnå støtte. Gennemgangen er baseret på den projektbeskrivelse, som ansøgerne har udarbejdet i forbindelse med deres ansøgning til Medicin- og behandlingspuljen.

1. Overførsel af ustekinumab fra mor til barn under graviditet og amning (Intra-uterine exposure to ustekinumab therapy)

During the past decade, medical treatment of IBD has become more advanced, including more specific immunomodulating drugs, also during pregnancy and lactation. Knowledge regarding pharmacokinetics during pregnancy, placental- and breastmilk transfer, and child development after drug exposure is crucial when counseling women in the fertile age. This research project will lead to more evidencebased counseling for the wellbeing of mother and infant. Further, insights into USK pharmakonetics during pregnancy will lead to optimization of treatment and potential reduced costs. Results from the present study will also be relevant for treatment of dermatologic and reumatologic disorders where USK is also prescribed.

Projektets hovedansøger er Mette Bykærholm Julsgaard, Aarhus Universitetshospital.
Deltagende regioner: Region Syddanmark, Region Sjælland, Region Hovedstaden, Region Midtjylland, Region Nordjylland.
Projektet har modtaget 1.367.399 kr. i tilskud fra Medicin- og behandlingspuljen.

2. Udvikling af non-kommerciel CAR T behandling til patienter med CD19 positiv hæmatologisk cancer

Behandling med CART-celler er en revolutionerende teknologi som har kunnet løfte overlevelse for fremskreden Akut lymfoblastær leukæmi fra 20 til 50%, og meget bemærkelsesværdigt med væsentligt nedsatte både kort- og langtids-bivirkninger, herunder væsentligt nedsat indlæggelsestid. Der er desuden lovende resultater med CART indenfor andre sygdomsgrupper, herunder myelomatose og lymfom.

Behandling med det patientspecifikke CD19 CART celleprodukt blev godkendt af EMA i 2019 til en afgrænset hæmatologisk patientgruppe og som den dyreste kræftmedicin nogensinde med en pris på ca 3 mio kr pr celleprodukt.
Produktionen af CART-celler er baseret på genetisk modifikation af patientens egne blodceller, hvilket er en omfattende proces der fordrer højteknologisk specialudstyr og særlige lokaler (GMO/GMP). I 2016 dannedes samarbejdsgruppen CIRCUIT, med deltagelse fra Rigshospitalet og Herlev Hospital. Gruppen har baggrund i CCIT-DK på Herlev Hospital og enhederne for allogen stamcelletransplantation på Rigshospitalet (Klinik for blodsygdomme, Børne-Unge-Afdelingen og Klinisk Immunologisk Afdeling).

Gruppen har nu etableret det teknologiske og videnskabelige grundlag for at åbne et akademisk investigator drevet klinisk forsøg med afprøvning af non-kommerciel CD19 CART. Patienter inkluderes nationalt og nordisk.
Det kliniske forsøg har til formål at etablere dokumentation for sikkerhed og effekt af non-kommerciel CD19 CART behandling i en udvidet hæmatologisk patientpopulation, med det formål på sigt at etablere fleksibel in house non-kommerciel CD19 CART behandling til kostpris (ca 10% af købspris). Dette vil medføre en markant besparelse for sygehusvæsenet foruden en fordel i hurtigere leverance og mulighed for at udvide indikationsområdet ved implementering af CART målrettet andre targets.

Den klinisk protokol på CD19 fase 1b studiet indsendes til lægemiddelstyrelsen og nationale videnskabsetisk komite i løbet af 2. kvartal 2021 mhp. behandling af den første patient inden udgangen af 2021. Dette fordrer dog en tilførsel af økonomi, primært mhp. produktionsomkostninger, etablering af nedfrysningsmuligheder under GMO/GMP-forhold, patientrelaterede procedure og overordnet projektstyring.

Projektets hovedansøger er Inge Marie Svane, Rigshospitalet.
Deltagende regioner: Region Syddanmark, Region Sjælland, Region Hovedstaden, Region Midtjylland, Region Nordjylland.
Projektet har modtaget 3.200.000 kr. i tilskud fra Medicin- og behandlingspuljen.

3. Opfølgningsprogram efter behandling for anal cancer - validering af ctDNA guided follow-up i forhold til billeddiagnostik.

NOAC 9 - A Phase II Randomised Nordic Anal Cancer Group Study on Circulating Tumor DNA guided Follow-Up

Squamous cell carcinoma of the anus is a rare disease, with less than 200 new cases in Denmark each year, but the incidence is increasing. The primary treatment modality is concomitant chemoradiotherapy (CRT) comprising high dose intensity-modulated radiotherapy (IMRT) based radiation therapy with combination chemotherapy. The overall response to treatment is excellent for the smaller tumors and less pronounced for high-risk tumors. The current overall treatment response and 5-year survival rate is still unknown for Danish patients, since we have no prospective clinical central database (Several applications from the DACG to RKKP rejected). Follow-up strategies are currently based on limited levels of evidence. The same applies to Sweden, where a national database has recently been launched and Norway also still pending prospective data collection (1-4).

A follow-up (FU) program for squamous cell carcinoma of the anus (SCCA) has 3 purposes; 1) to detect lack of complete response to primary treatment, 2) early detection of local or distant recurrence and 3) to describe and manage late morbidity. Currently, there are no clinical trials that have investigated the optimal FU strategy for SCCA and consequently attempt to standardize FU for these patients are hampered by an obvious lack of evidence. FU has not been standardized between the treating centers, nor between the Nordic countries, but is based on local tradition and experience.

The Danish Anal Cancer Group (DACG) has recently provided a national guideline for FU after SCCA (DACGnet.dk) with the above purposes to ensure equality for patients treated in the three Danish centers. However, to validate a new standardized strategy, prospective data collection is needed. Furthermore, tools for early detection of recurrences, use of advanced imaging and fast track into late morbidity clinics, should be investigated. Finally, investigations to validate most rational follow-up programs should be highly prioritized. Unnecessary visits, radiation exposure, worries and costs should be reduced, and optimal surveillance introduced for high risk patients.

Projektets hovedansøger er Karen-Lise Garm Spindler, Herlev-Gentofte Hospital.
Deltagende regioner: Region Midtjylland, Region Syddanmark, Region Hovedstaden.
Projektet har modtaget 1.530.000 kr. i tilskud fra Medicin- og behandlingspuljen.

4. Bacterial interference for preventing recurrent urinary tract infection – New ways of treatment.

Urinary tract infection (UTI) is one of the most common bacterial infections, affecting 150 million people each year worldwide. UTIs account for high antibiotic consumption and major social- and healthcare costs. Currently, there

is a great media exposition on benign urology especially UTI. Using our newly developed animal model, we have a unique way to investigate experimental UTI. Combining animal studies with a clinical study, this PhD elucidate alternative treatment methods for recurrent urinary tract infection.

Projektets hovedansøger er Karin Andersen, Odense Universitetshospital.
Deltagende regioner: Region Syddanmark, Region Midtjylland, Region Nordjylland.
Projektet har modtaget 650.000 kr. i tilskud fra Medicin- og behandlingspuljen

5. Treatment effects of Bisoprolol and Verapamil in symptomatic patients with non-obstructive hypertrophic cardiomyopathy - TEMPO II.
The scientific aim of this study is to conduct a Danish investigator-initiated multi-centre double-blinded randomized placebo-controlled cross-over trial to compare the treatment effects of Bisoprolol (beta 1 receptor specific beta blocker (BB)) and Verapamil (cardio-specific calcium channel blockers (CCB)) in 140 patients with non-obstructive hypertrophic cardiomyopathy (HCM).

The guideline-recommended medical treatments with non-dilating BB or cardio-specific CCB for symptomatic HCM patients has never been systematically evaluated (1). Conducting trials evaluating the effects of BB and CCB in HCM have no direct industrial or commercial purpose, and no industry supported trials are expected. The lack of evidence is a daily clinical problem that is aggravated by a recent positive phase three trial (EXPLORE-HCM) on a new HCM specific drug, Mavecamten(2). Mavecamten is expected to be approved by authorities based on higher level of evidence, than what is available for BB and CCB. Comparative studies between Mavecamten and BB or CCB, respectively, have not been performed, and are not of commercial value for the Mavecamten patent holders. Therefore, we risk introducing a new and expensive treatment without evidence for the treatment effects of existing treatments options.

HCM is an inherited myocardial disease affecting up to 10.000 Danes. HCM can cause lifelong heart failure symptoms and devastating complications including sudden death due to myocardial hypertrophy and dysfunction. The survival is usually good in HCM patients, but modification of symptoms and risk factors are important clinical aims.

Projektets hovedansøger er Morten Steen Kvistholm Jensen, Aarhus Universitetshospital.
Deltagende regioner: Region Syddanmark, Region Hovedstaden, Region Midtjylland, Region Nordjylland.
Projektet har modtaget 3.543.000 kr. i tilskud fra Medicin- og behandlingspuljen

6. Antibiotikaprofylakse til brystrekonstruktion med implantater: et fase III randomiseret kontrolleret multicenterstudie.
Projektets formål er at sikre evidens-baseret brug af antibiotikaprofylakse til kvinder, der får implantatbaseret brystrekonstruktion. Mange kirurger vælger at skylle implantater og implantatrum med en blanding af gentamicin, vancomycin og cefazolin, men effekten er aldrig undersøgt i et randomiseret kontrolleret forsøg. Derfor vil vi undersøge, om den lokale antibiotikabehandling kan mindske risikoen for infektion og tab af rekonstruktion i et randomiseret kontrolleret multicenterforsøg. Vi vil desuden undersøge, om der er bivirkninger til behandlingen, herunder om der udvikles antibiotikaresistens.

Projektets hovedansøger er Mikkel Herly, Rigshospitalet.
Deltagende regioner: Region Hovedstanden, Region Sjælland, Region Syddanmark.
Projektet har modtaget 1.999.724 kr. i tilskud fra Medicin- og behandlingspuljen

7. Et randomiseret fase III forsøg med lomustine versus lomustine og bevacizumab til patienter med tilbagefald af glioblastoma multiforme (GBM).
At undersøge om bevacizumab i en selekteret patientgruppe øger overlevelsen i kombination med lomustine i forhold til behandling med lomustine alene til patienter med tilbagefald af GBM.

Indikation for eksperimentel behandling
Anden linje behandling til patienter med tilbagefald af GBM, med PS 0-1, unifokal sygdom, prednisolon ≤ 25 mg og som udtrykker methyleret angiotensinogen promoter region.

Projektets hovedansøger er Ulrik Lassen, Rigshospitalet
Deltagende regioner: Region Hovedstaden, Region Syddanmark, Region Nordjylland.
Projektet har modtaget 2.116.000 kr. i tilskud fra Medicin- og behandlingspuljen

8. ithium versus cariprazine in the acute phase treatment of bipolar depression: a pragmatic head-to-head open, randomized multicenter study. The 9th study of the Danish University Antidepressant Group (DUAG 9).
Bipolar disorder is a recurrent, often lifelong and complex disorder, characterized by manic and
depressive episodes. Depression is the dominant pole, reported to occupy more than 50 % of the time in patients with bipolar disorder type 2 and 32 % in type 1 (Judd et al. 2003).
Lithium was the first mood stabilizer and still has an important role in acute and maintenance treatment of bipolar disorder (Licht 2012). While the positive data on maintenance treatment of bipolar disorder and on acute treatment of mania

is robust (Grunze et al. 2009, 2013), the data regarding lithium's effect in the acute treatment of bipolar depression is conflicting (Grunze et al. 2010). In eight out of nine small older studies lithium was found to be superior to placebo in the acute treatment of bipolar depression, and similar to tricyclic antidepressants in three other relatively small studies (Zornberg et al. 1993). These latter studies, however, were underpowered (Licht 2012). In a more recent, large industry sponsored randomized study (Young et al. 2010) the efficacy of two doses of quetiapine (300 mg and 600 mg) was tested against placebo for the acute treatment of bipolar depression (type 1 and 2) with a lithium arm incorporated to ensure the assay sensitivity. Both doses of quetiapine were statistically significantly superior to placebo at week 8, but lithium was not. One limitation of the study was that relatively low serum concentrations of lithium, with the mean of individual patient's median se-lithium being 0.61 mmol/l, and with 35% of patients never reaching the aimed level at 0,6 mmol/l. However, a post hoc analysis including only patients with a median se-lithium above 0.8 mmol/l also revealed no difference in antidepressant effect when compared to the placebo group. A recent 12-week randomized comparison of lithium and venlafaxine monotherapy for acute treatment of depression in bipolar type 2 disorder (Amsterdam et al. 2016) demonstrated superiority of venlafaxine with response proportions of 67.7 % and 34.4 % among the venlafaxine treated and the lithium treated patients, respectively. There was no between-group difference in hypomanic symptom severity. Interestingly, the investigators aimed at achieving a relatively high serum concentration of lithium at 0.8 to 1.5 mmol/l and obtained a mean maximum concentration of 0.94 mmol/l. The observed drop-out was higher in the lithium-treated group as compared to the venlafaxine treated group, which might be related to the relatively high lithium concentrations.

Despite the uncertainty as to what extent lithium is an effective acute treatment for bipolar depression, it is recommended as a first-line monotherapy in many treatment guidelines, including Danish guidelines (RADS 2015). A major reason for this is the strong positioning of lithium as a maintenance treatment, providing rational for introducing lithium already in the acute treatment phase. Also, due to the relatively few available options for the acute pharmacotherapy of bipolar depression (Grunze et al. 2010), lithium with its relatively beneficial side effect profile and its unique pharmacological mode of action fits well into the armamentarium.

Due to the discrepancy between the conflicting evidence and the recommendation in guidelines regarding lithium as an acute treatment of bipolar depression as outlined above, and thereby the uncertainty of the role of lithium in clinical practice as an acute treatment of bipolar depression, we find it clinically relevant pragmatically and under conditions mimicking clinical routine to compare lithium with a drug that has well-documented efficacy.

As comparator we chose cariprazine, a novel atypical antipsychotic, recently available in Denmark and licensed in the USA for the acute treatment of depression as part of bipolar disorder type 1 for the following reasons: cariprazine has a well-documented efficacy as outlined in the following, it is

relatively well tolerated, and because of its novelty, only few patients will be treated with the drug in the period up till study start, which may facilitate recruitment. Cariprazine has demonstrated efficacy compared to placebo in the acute treatment of depression in bipolar disorder type 1 in three randomized trials (Durgam et al. 2016, Earley et al. 2019a and 2019b) without inducing or worsening manic symptoms (Mcintyre et al. 2019). One placebo-controlled flexible-dose phase 2 trial conducted in 2010 was negative (Yatham et al. 2020). The patient sample of the latter study consisted of both bipolar type 1 and type 2 patients. The authors noted that the sample size was small, that a group received an ineffective low-dose of cariprazine (0.25 - 0.75 mg daily) and that one-quarter of the study population had bipolar disorder type 2. For the subsequent phase 2b and 3 studies, a higher dose of cariprazine was used (1.5 - 3.0 mg), the study populations were restricted to bipolar disorder type 1 patients, and the studies were well powered, each with twice the number of randomized patients as compared to the original study. In addition, a more gradual dose titration was used to minimize akathisia and early discontinuation. Cariprazine has furthermore demonstrated efficacy in the acute treatment of mania including mixed mania (Sachs et al. 2015, Durgam et al. 2015, Calabrese et al. 2015).

Projektets hovedansøger er Sune Puggaard Vogt Straszek, Aalborg Universitetshospital.
Deltagende regioner: Region Syddanmark, Region Sjælland, Region Hovedstaden, Region Nordjylland.
Projektet har modtaget 1.767.790 kr. i tilskud fra Medicin- og behandlingspuljen

9. OPTIMAL - Individualiseret dosistitrering af biologisk behandling til svær astma.

Biologiske lægemidler repræsenterer en ny og revolutionerende behandling af svær astma, som er en kronisk og svært invaliderende sygdom. En stor del af patienterne, som får denne behandling, har hurtig og eklatant effekt af den. Data fra DSAR viser at 60 % af patienterne efter et års behandling har opnået at blive fri for astmaforværringer og behov for daglig behandling med binyrebarkhormon tabletter. Biologisk behandling er dog ekstremt omkostningstung. Lægemidlerne er meget dyre og behandlingen kræver at patienterne møder fast på hospitalet til injektioner med ugers mellemrum. De gives i standardiseret dosis i faste intervaller til alle patienter uanset sygdomskontrol.
OPTIMAL er, som det første studie, igang med at undersøge om doseringen af biologisk behandling kan tilpasses til den enkelte patients behov på det givne tidspunkt. OPTIMAL vil afklare om patienter, der har opnået god sygdomskontrol, kan klare sig med færre behandlinger og dermed mindre medicin. Vi vil undersøge, om vi kan bruge en fastlagt algoritme til at titrere behandlingen med biologiske lægemidler, således at der skrues ned for

behandlingen når patienten kan tåle det, mens der skrues op igen ved tegn til begyndende tab af sygdomskontrol. Således sikres det at patienten får mindst mulig behandling uden tab af sygdomskontrol.

Forventet impact af OPTIMAL projektet
For patienten: Minimering af hospitalsbesøg og medicin og samtidig optimering af behandlingseffekt ifm biologisk behandling
For klinikeren: Rationalisering af patientbehandlingen med udvikling af et evidensbaseret værktøj til klinisk beslutningstagen
For samfundet: Væsentlig reduktion af udgifter til biologisk behandling, som aktuelt koster 150.000 kr per patient årligt alene for lægemidlet. Hertil skal tillægges udgifter fra de hyppige hospitalsbesøg ifm behandlingerne. Således forventes resultaterne fra OPTIMAL studiet på sigt at kunne frigive væsentlige ressourcer, der kan bruges på andre indsatser.

Projektets hovedansøger er Celeste Porsberg, Bispebjerg Hospital.
Deltagende regioner: Region Syddanmark, Region Hovedstaden, Region Midtjylland, Region Nordjylland.
Projektet har modtaget 1.030.651 kr. i tilskud fra Medicin- og behandlingspuljen

10. Effekten af SGLT2-hæmning på nyrefunktion, renal hæmodynamik og vasoaktive hormoner hos patienter med type 2 diabetes med og uden kronisk nyreinsufficiens og patienter med non-diabetisk kronisk nyreinsufficiens.
En ny type medicinsk behandling af type 2 diabetes (DM2), de såkaldte SGLT2-hæmmere (sodium glucose cotransport type 2 inhibitors, SGLT2i) er vist markant at mindske risikoen for hjertekarsygdom og nyresvigt hos både patienter med DM2 og patienter med kronisk nyresvigt af andre årsager en diabetes, men årsagerne hertil er ukendte.

Formålet med projektet er at forbedre behandlingen af kronisk nyresvigt ved at udforske disse årsager. Virkningen undersøges hos patienter med forskellige grader af kronisk nyresvigt, her i blandt patienter med fremskreden nyresvigt (eGFR ned til 20 ml/min), både med og uden samtidig diabetes.

Projektets hovedansøger er Steffen Flindt Nielsen, Regionshospitalet Holstebro.
Deltagende regioner: Region Syddanmark, Region Midtjylland.
Projektet har modtaget 975.900 kr. i tilskud fra Medicin- og behandlingspuljen

11. Forlængelse af DOSeringsintervallet ved behandling af kronisk spontan urticaria med OMAlizumab (SODOMA)
Projektets formål er at undersøge om patienter med kronisk spontan urticaria (nældefeber), som er velbehandlede med det biologiske lægemiddel omalizumab (anti-IgE) i en dosering på 300 mg subkutant hver 4. uge

(standardbehandling) kan intervalforlænges med bibeholdelse af samme grad af sygdomskontrol.

Projektets hovedansøger er Jennifer Astrup Sørensen, Bispebjerg Hospital.
Deltagende regioner: Region Hovedstaden, Region Midtjylland.
Projektet har modtaget 1.17.000 kr. i tilskud fra Medicin- og behandlingspuljen