Celecoxib

Mutations in the tumor suppressor gene NF2 lead to Neurofibromatosis type 2 (NF2), a tumor predisposition syndrome characterized by the development of schwannomas, including bilateral vestibular schwannomas with complete penetrance. Recent work has implicated the importance of COX-2 in schwannoma growth. Using a genetically engineered murine model of NF2, we demonstrate that selective inhibition of COX-2 with celecoxib fails to prevent the spontaneous development of schwannomas or sensorineural hearing loss in vivo, despite elevated expression levels of COX-2 in Nf2-deficient tumor tissue. These results suggest that COX-2 is nonessential to schwannomagenesis and that the proposed tumor suppressive effects of NSAIDs on schwannomas may occur through COX-2 independent mechanisms [1].

Chronic subdural hematomas (cSDHs) have shown an increasing incidence in an ageing population over the last 20 years, while unacceptable recurrence rates of up to 30 % persist. The chronic subdural hematoma recurrence rate seems to be related to the excessive neoangiogenesis in the parietal membrane, which is mediated via vascular endothelial growth factor (VEGF). This is found to be elevated in the haematoma fluid and is dependent on eicosanoid/prostaglandin and thromboxane synthesis via cyclooxygenase-2 (COX 2). With this investigator-initiated trial (IIT) it was thought to diminish the recurrence rate of operated-on cSDHs by administering a selective COX-2 inhibitor (Celecoxib) over 4 weeks' time postoperatively in comparison to a control group.

The thesis of risk reduction of cSDH recurrence in COX-2-inhibited patients was to be determined in a prospective, randomised, two-armed, open phase-II/III study with inclusion of 180 patients over a 2-year time period in four German university hospitals. The treated- and untreated-patient data were to be analysed by Fisher's exact test (significance level of alpha, 0.05 [two-sided]).

After screening of 246 patients from January 2009 to April 2010, the study had to be terminated prematurely as only 23 patients (9.3 %) could be enrolled because of on-going non-steroid anti-rheumatic (NSAR) drug treatment or contraindication to Celecoxib medication. In the study population, 13 patients were treated in the control group (six women, seven men; average age 66.8 years; one adverse event (AE)/serious adverse event (SAE) needing one re-operation because of progressive cSDH (7.7 %); ten patients were treated in the treatment group (one woman, nine men; average age 64.7 years; five AEs/SAEs needing two re-operations because of one progressive cSDH and one wound infection [20 %]). Significance levels are obsolete because of insufficient patient numbers.

The theoretical advantage of COX-2 inhibition in the recurrent cSDH could not be transferred into the treatment of German cSDH patients as 66.6 % of the patients showed strict contraindications for Celecoxib. Furthermore, 55 % of the patients were already treated with some kind of COX-2 inhibition and, nevertheless, developed cSDH. Thus, although conceptually appealing, an anti-angiogenic therapy with COX-2 inhibitors for cSDH could not be realised in this patient population due to the high prevalence of comorbidities excluding the administration of COX2 inhibitors [2].

1)
Wahle BM, Hawley ET, He Y, Smith AE, Yuan J, Masters AR, Jones DR, Gehlhausen JR, Park SJ, Conway SJ, Clapp DW, Yates CW. Chemopreventative celecoxib fails to prevent schwannoma formation or sensorineural hearing loss in genetically engineered murine model of neurofibromatosis type 2. Oncotarget. 2017 Oct 24;9(1):718-725. doi: 10.18632/oncotarget.22002. eCollection 2018 Jan 2.

PubMed PMID: 29416648; PubMed Central PMCID: PMC5787503.
2)

Schaumann A, Klene W, Rosenstengel C, Ringel F, Tüttenberg J, Vajkoczy P. COXIBRAIN: results of the prospective, randomised, phase II/III study for the selective COX-2 inhibition in chronic subdural haematoma patients. Acta Neurochir (Wien). 2016 Nov;158(11):2039-2044. PubMed PMID: 27605230.