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Immunoadsorption in Buerger'S Disease (Thromboangiitis Obliterans): A Promising Therapeutic Option: Results of a Consecutive Patient Cohort Treated in Clinical Routine Care

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Abstract

Background: Buerger`s disease (TAO, thrombangiitis obliterans) is an inflammatory vessel disease affecting small and medium sized arteries and veins leading to acral or limb-threatening ischemia syndromes and/or thrombophlebitis with high amputation rates. Immunhistopatholocical and serological data let to the new paradigm of an immunopathogenesis of TAO. Based on this hypothesis immunadsorption (IA) was successfully introduced into the therapeutic spectrum and the presence of G-protein coupled autoantibodies in TAO and their successful elimination by IA was shown.

Objective: We present an update of the results of our observational cohort study including patients suffering from TAO consecutively treated by IA in clinical routine care.

Patients and methods: From December 2012 to February 2016 twenty-two patients suffering from TAO were treated with IA in our institution. Retrospectively, three patients had to be excluded (finding of an elevated Lp(a)-concentration, presence of atherosclerotic coronary lesions, loss of blood sample) leaving 19 patients for final analysis (17 male, 2 female; mean age 40 (20-54) years). IA was performed during a five-day course with Fesenius-GlobaffinR-adsorbers and an intended clearance of the 2.5-fold plasma volume. G-protein coupled -AAB were analyzed using specific commercially available ELISA techniques. Clinical follow-up included regular outpatient visits and/or telephone-contacts for patients living in more remote areas. Data is presented by descriptive statistics.

Results: G-protein receptor autoantibodies (AAB) were present in 14 of our patients (74%), with 1 AAB in 5 and multiple AAB in 9 patients. The presence of a clustering of AAB directed against the α1-receptor and endothelin A-receptor was seen in 9 out of the 14 AAB-positive patients (64%). AAB directed against ET-A-receptors never appeared without AAB directed against the α1-receptor and were exclusively directed against the extracellular receptor-loop 1. Immediately after a five day course of IA, 12 out of 14 AAB-positive patients were free of AAB (85%). Follow-up data was available in 15 patients. During a mean follow-up period of 3 month (0-35 month) there were no disease flairs. In all but one patient skin lesions healed. Pain scale values decreased from 7.0 (5-9) to 2.0 (0-5). Minor amputations already anticipated before IA were performed in two patients without complications. Only one patient underwent major-amputation after a failed surgical bypass procedure of doubtful indication with prior subcritical forefoot-tcpO2-values during follow-up in our institution. There was a high rate of smoking cessations (13 active smokers before IA, 3 during last follow-up) due to a close monitoring and admonition.

Conclusion: Although the exact rote of G-protein coupled receptor-AAB in TAO has yet to be defined, we were able to reproduce our formerly published results of a clustering of these AAB and their successful elimination by IA in this larger cohort, which anticipated a beneficial clinical course. IA might be able to stabilize the disease course, but the unusual high rate of smoking cessations made it impossible to exactly define its exact contribution on clinical outcome.

Keywords: Buerger`s disease; Thrombangiitis obliterans; Thromboangiitis obliterans; G-protein coupled receptor; Autoantibodies; Vasculitis

Introduction

Buerger`s disease (TAO, thromboangiitis obliterans) is an inflammatory vessel disease affecting small and medium sized arteries and veins [1]. The inflammation induces vessel occlusions by formation of mononuclear cell rich thrombi, leading to acral or limb-threatening ischemia syndromes and/or thrombophlebitis [2,3]. Amputation rates are as high as 75% for minor and 30% for major amputations [4]. Although the ethiology of TAO is still unknown tobacco use is considered to be an indispensible trigger-mechanism [2,3].

Pathohistological and immunhistological findings, the detection of increased autoantibody concentrations, and evidence for cytokine activation finally led to the new paradigm of an immunopathogenesis of TAO, first published by Ketha SS and Cooper LT in 2013 [5].

Based on the hypothesis that TAO is an immunmediated disease with humoral factors may play an important pathogenetic role immunadsorption (IA) was successfully introduced in a pilot study by Baumann et al. and later introduced into clinical routine by the corresponding author [6,7]. In 2014 we first described the detection of G-protein coupled receptor autoantibodies in patients with TAO and their removal by IA [8]. Here we present an update of the results of our ongoing clinical project including the results of a clinical follow-up analysis.

Patients and Methods

From December 2012 to February 2016 twenty-two patients suffering from Buerger`s disease were treated with IA in our institution and included in this observational cohort-study. Retrospectively, diagnosis of TAO was corrected in two patients due to the finding of an markedly elevated Lp(a) concentration resp. the detection of atherosclerotic coronary lesions. In another patient baseline blood samples got lost on transport to the laboratory, leaving 19 patients for final analysis.

Clinical characteristics are presented in Table 1. All patients had already been treated with best medical treatment including intravenous prostanoid infusions (Iloprost and/or PGE1) prior to IA without clinically satisfactory results. IA was performed during a five-day course with Fesenius-GlobaffinR-adsorbers (Fesenius Medical Care AG & Co KGaA, Bad Homburg v.d. Höhe, Germany) and an intended clearance of the 2.5-fold plasma volume. G-protein coupled - AAB were analysed by E.R.D.E-AKK-Diagnostik GmbH, Berlin, Germany, using peptides corresponding to the first and/or second extracellular loop of α1, Endothelin A, Angiotensin II Type 1, protease activated receptor (PAR) 1/2. Peptides were coupled to pre-blocked streptavidin-coated 96-well plates (Perbio Science, Bonn, Germany). Patient serum was added in a 1:100 dilution and incubated for 60 min. As detection antibody a horseradish peroxidase conjugated anti-human IgG antibody was used (Dianova, Hamburg, Germany). Antibody binding was visualized by the 1-Step Ultra TMB ELISA (Perbio Science, Bonn, Germany). The absorbance was measured at 450 nm with a SLT Spectra multiplate reader (TECAN, Crailsheim, Germany). Clinical follow-up included regular outpatient visits and/or telephone-contacts for patients living in more remote areas. Descriptive statistics were applied.

Results

Overall, G-protein receptor auto-antibodies (AAB) were present in 14 of all patients (74%), with one AAB in 5, 2 AAB in 7, 3 AAB in 1 and 4 AAB in 1 patient(s). The presence of a clustering of AAB directed against the α1-receptor and endothelin A-receptor was seen in 9 out of the 14 AAB-positive patients (64%). AAB directed against ET-A-receptors never appeared without AAB directed against the α1-receptor and were exclusively directed against the extracellular receptor-loop 1.

After IA at day 5, 12 out of 14 AAB-positive patients were free of AAB. In two patients AAB persisted, while in two others AAB undulated with negative results immediately after IA and re-occurrence next day before re-starting. Even if these cases were considered as elimination-failures, in the vast majority of our patients (71%) AAB against G-protein-receptors were successfully eliminated by the 5 day course of IA.

Clinical follow-up data was available in 15 patients. There were no disease flares. Median visual analog pain-scale (VAS) values improved from median 7.0 (5-9) before IA to 2.0 (0-5) during last follow-up visit. All patients received pain medication before IA. During last follow-up only 2 patients continued to take opioids, while four patients - including one patient suffering from spondylarthritis- took NSAR. In all but one patient skin lesions heeled. Minor amputations - already anticipated before IA - were performed in two patients. Only one patient underwent unexpected major-amputation after a failed pedal bypass procedure of doubtful indication in case of a wound infection with prior subcritical forefoot-tcpO2-values during the last follow-up visit prior to the operation in our institution. 10 patients returned to their former work or education, 4 retired early, one was still on sick leave. Before IA there were 13 active and 6 recently quitting former smokers, during last follow-up there were 12 non-smokers and only 3 active smokers.

Discussion

AAB directed against G-protein coupled receptors are increasingly recognized as modulators of various cardiovascular pathologies and diabetes mellitus [9-11]. Their prevalence in these conditions varies grossly von 30 to 60%. With our increasing cohort we were able to reproduce preliminary findings showing almost the same range of positive AAB-analyses. Furthermore, we were able to reproduce the predicted clustering of AAB directed against α1-receptor and endothelin A-receptors, which might be of special pathophysiologic interest as both receptors mediate strong vaso constrictive actions consistently with the clinical finding of a strong tendency towards vasospasms in these patients. Deviant unphysiologic and prolonged activation of post-receptor-actions by G-protein coupled AAB have been published and the pathogenic potential of these circulating AAB has already been elucidated in animal models as well as in clinical studies [12-18]. We were able to confirm, that IA successfully eliminated the vast majority of the AAB in a five-day course, with the majority of the eliminations occurring within the first two to three sessions.

More acute beneficial effects of IA in Buerger`s disease have been published and cover a marked improvement in pain, an improvement of digital pulse curves, an incline in tcpO2 and a decline in tcCO2-levels, and – even more important clinically – ulcer healing [6]. Our results indicate that IA might also improve and stabilize the subsequent clinical course of the disease. However, the beneficial outcome was certainly co-influenced by an unusual high rate of smoking cessation in our cohort, making it impossible to define the exact impact of IA on outcomes. Nevertheless, in many cases clinical improvement after IA was observed before smoking was stopped.

Patient, initials	Age (y)	Sex	Duration of disease (y)	Smoking status (cigarettes)	Ischemic rest pain, visual analog pain scale result	Active ulcer/ gangrene/skin lesions	Former amputation	Thrombo-phlebitis	Raynaud`s phenomenon	Other diseases
1 NA	40	male	2	active	VAS 7	D ped I, II left	-	-	yes	pulmonary embolism 2008
2 LH	53	male	3	active	VAS 6	D II right	-	-	yes	acute gastritis and duodenitis, extirpated basalioma, mild hypercholesterolemia
3 MM	48	female	4	active	VAS 9	left forefoot	D IV and V left as well as partial amputations D I, II ped left	-	-	-
4 NC	39	male	2	former	VAS 7	D I right	D I ped left	-	-	-
5 RT	42	male	2	former	VAS 9	dehiscent amputation wounds	below-knee right, Dig V transmeta-tarsal left, dig ped II left	-	-	drug-induced mild leucopenia and thrombopenia
6 RD	20	male	1,5	active	VAS 8	left forefoot, toes right	-	-	-	cannabis abuse
7 VK	52	male	4	active	VAS 7	toes right foot	-	-	yes	occluded distal arterial bypass
8 BS	26	male	1	active	VAS 8	D I ped left	-	-	yes	additional cannabis abuse, penicillin allergy, seronegative spondylathritis
9 FB	50	male	2	active	VAS 7	D II,V ped left	-	yes	-	acute forefoot-infection; alcoholism, mild hypertension
10 BR	27	male	1	active	VAS 8	DI ped right	-	-	-	-
11 HU	51	male	3	former	VAS 9	amputation wound left forefoot	right lower leg, recently left forefoot	-	-	-
12 OC	54	male	1	active	VAS 8	D II and III right, Dig IV and V left	-	-	-	pediculosis capitis and scapies
13 MR	37	male	1	former	VAS 6	-	recently Dig II right hand, Dig ped II, III right, Dig ped I, II left	-	-	-
14 BM	32	male	1	former	VAS 6	-	-	yes	yes	-
15 vSP	38	male	1	active	VAS 5	-	Dig III left	-	-	
16 TC	34	male	2	active	VAS 7	-	-	-	-	-
17 BZ	52	male	2	active	VAS 6	-		yes		
18 EM	49	female	1	former	VAS 8	D II, IV right hand; D I, II left hand	-	-	-	-
19 WD	33	male	3	active	VAS 6	D III ped left	D I ped left	-	yes	-

Mean	40	n:f=17:2	2,0	13 active, 6 former smokers	VAS 7.0	-	-	-	-	-

Table 1: Clinical characteristics of our cohort.

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