Obinutuzumab in connective tissue diseases after former rituximab-non-response: a case series

In the following case series, we present four patients with different connective tissue diseases (CTD) showing a remarkably positive response on treatment with Obinutuzumab despite former rituximab-non-response in three cases. Demographic data including, age, gender, disease duration, type of involvement, previous as well as concomitant treatments are shown in table 1. Efficacy of treatment was assessed by clinical, laboratory and radiologic findings or global patient assessment for rheumatological symptoms, respectively. Clinical response was defined by an improvement of involved organ functions as well as a reduction of the severity of symptoms. Global tolerance was evaluated.

SLE

Two patients with SLE and active glomerulonephritis were treated with Obinutuzumab after rituximab failure. One patient each additionally suffered from antiphospholipid syndrome and neuropsychiatric lupus, respectively. After one cycle with obinutuzumab (1 g, day 0, 14), both patients came off dialysis and showed a stable kidney function over a time period of at least 6 months. One patient had cardiac involvement and highly elevated NT-pro-BNP which markedly decreased after treatment with obinutuzumab. Serological markers such as anti-ds-DNA antibodies and C3-complement consumption strongly improved after therapy.

ANTI-JO1 SYNDROME

We further included a patient with anti-Jo1-syndrome who did not respond to her previous treatments including Rituximab, IVIG, Cyclophosphamide and repeated prednisolone pulse therapies. Her disease was manifested by myositis (creatine-kinase (CK) max. 8946 U/L) and CT-confirmed interstitial lung disease with a decreased CO-diffusion capacity of 57.3% expected. After one cycle of obinutuzumab, muscle weakness improved and CK and lactate dehydrogenase levels markedly decreased.

CREST SYNDROME

In this patient, CREST syndrome was diagnosed with sclerodactyly, Raynaud's phenomenon, oesophageal hypomotility, teleangiectasia, calcinosis cutis and pulmonary arterial hypertension and an ANA-titre of 1:10 000 in 2006. In 2013, she

Table 1 Patient demographics and history of diseases and treatments

	SLE 1	SLE 2	Anti-Jo1 syndrome	CREST-syndrome/CLL
Age	33	52	46	80
Gender	F	F	F	F
Year of diagnosis	2019	2008	2019	2006/ 2013
Clinical manifestations	Nephritis, polyserositis, pancytopaenia, pancarditis	Nephritis, CNS-involvement, Libman-Sacks endocarditis, APS, ILD	Myositis, ILD	Sclerodactylia, teleangiectasia, Raynaud's, PAH, calcinosis cutis
Previous therapies and dosage of prednisolone before treatment with OBI	CYC 6×500 mg i.v., MPA, RTX 2×1 g i.v. twice within 6 months; prednisolone 80 mg/d	CYC 6×500 mg i.v., MPA, RTX 2×1 g i.v. twice within 6 months, IVIG, plasmapheresis; prednisolone 70 mg/d	CYC 6×750 mg i.v., RTX 2×1 g i.v., IVIG; repeated prednisolone pulse therapies starting with 80 mg/d	SSZ, MTX, HCQ
Characteristic findings before treatment with Obinutuzumab	Crea 3,14 mg/dL, dialysis, erythrocyturia 3327 /µL, anti-ds-DNA ab. (RIA) 15128,6 IU/mL, C3 0,28 g/L, anti-nucleos. ab. 130,9 IE/mL, nt-pro BNP 42 526 ng/L, SLEDAI-2K: 30	Crea 4,97 mg/dL, dialysis, Prot. Urine/ Crea Urine 108,27 g/molKr, anti-ds-DNA ab. (RIA) 2,5 IU/mL, SLEDAI-2K: 32	myalgia, muscle weakness, dyspnoea, CK 8946 U/L, LDH 910 U/L, CRP 13,9 mg/L	calcinosis cutis, PA 65/30/43 mmHg, PC 13 mmHg, PAR 393 dyn.sec.cmˆ–5, CI 3,3 l/min*m², VC in 75,6%, FEV1 71,0%, FVC 81,2%, TLC 85,6%, Rtot 96,4%, DLCOc SB 49,7%, DLCOc/VA 73,6%"
Characteristic findings after treatment with Obinutuzumab	Crea 1,3 mg/dL, no dialysis, erythrocyturia 258 /µL, anti-ds-DNA ab. (RIA) 224,9 IU/mL, C3 0,83 g/L, anti-nucleos. ab. 20,2 IE/mL, nt-pro BNP 520 ng/L, SLEDAI-2K: 2	Crea 1,95 mg/dL, no dialysis, Prot. Urine/Crea Urine 57,16 g/molKr, anti-ds-DNA ab. (RIA) 2,5 IU/mL, SLEDAI-2K: 17	myalgia and muscle weakness strongly diminished, no dyspnoea, CK 188 U/L, LDH 221 U/L, CRP 4,1 mg/L	calcinosis cutis disappeared, VC in 85,5%%, FEV1 82,9%, FVC 90,7%, TLC 93,5%, Rtot 84%, DLCOc SB 49,3%, DLCOc/VA 69,2%
Co-medication during treatment with OBI and dosage of prednisolone after treatment with OBI at last follow-up	MPA 360 mg 2-0-2, HCQ 200 mg 1-0-0, prednisolone 3 mg 1-0-0	MPA 360 mg 2-0-2, HCQ 200 mg 1-0-0, prednisolone 5 mg 1-0-0	AZA 50 mg 1-1/2-1, prednisolone 5 mg 1-0-0	macitentane 10 mg 1-0-0, chlorambucile, bendamustine
Global tolerance	No major side effects	No major side effects	No major side effects	No major side effects

BNP, brain natriuretic peptide; CK, creatine-kinase; CLL, chronic lymphocytic leukaemia; CREST, Calcinosis cutis - Raynaud's phenomenon - Esophageal dysmotility - Sclerodactylia - Teleangiectasia; CRP, C reactive protein; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HCQ, hydroxychloroquine; ILD, interstitial lung disease; i.v, intravenous; IVIG, intravenous immunoglobulins; LDH, lactate dehydrogenase; MPA, mycophenolic acid; MTX, methotrexate; OBI, obinutuzumab; PAH, pulmonary arterial hypertension; RIA, radioimmunoassay ; SLE, systemic lupus erythematosus; SSZ, sulfasalazine.

developed chronic lymphocytic leukaemia requiring a B-cell depleting treatment for which obinutuzumab was chosen in accordance with current national and European guidelines.

After two cycles of obinutuzumab, the patient had a complete remission of the haematological disease and showed diminishing calcinosis cutis which gradually disappeared completely until the end of the treatment.

CONCLUSION AND PHARMACOLOGICAL CONSIDERATIONS

Obinutuzumab has recently been proven as an effective option in proliferative lupus nephritis leading to significantly better renal response compared with placebo.[1] The data presented here suggest an efficacy of obinutuzumab in different CTD even after failure of rituximab. We hypothesise that the low dependency of complement factors, the altered mechanisms of action including enhanced antibody-dependent cellular cytotoxicity (ADCC) of obinutuzumab and its presumably enhanced efficacy in inflamed tissues are factors supporting our hypothesis that obinutuzumab should be studied in various CTD after rituximab failure, but especially as first-line biologic after failure of conventional disease-modifying antirheumatic drugs (DMARDs).[2–5]

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