Appendix 3

Overview of studies on the use of TNF-α inhibitors in sarcoidosis

Randomized placebo controlled trials

Authors	Drug	Study goal	Patients treated (n)	Outcome	Drop-outs (n)	Organ involvement	Combi/ monotherapy	Dosage	Adverse effects
Baughman et al. (2006)[1]	Infliximab	To assess the efficacy of infliximab in pulmonary sarcoidosis, multicentre study	138 (46 infliximab 3 mg/kg, 47 infliximab 5 mg/kg, 45 placebo)	Significantly higher increase in FVC% from baseline to week 24 in infliximab group (3 and 5 mg/kg) compared to placebo (p=0.038); no improvement in dyspnea, 6MWD, skin abnormalities (LuPGA); patients with more severe disease tended to benefit more from infliximab	2 in infliximab 3 mg/kg group, 2 in infliximab 5 mg/kg, 1 in placebo group. Reasons: withdrawal of consent, unable to draw blood, lost to follow-up	Lungs, skin, eye	Combination with GC n=70, immunomodu-lation n=10, GC/immuno-modulation n=58. No difference between groups.	3 or 5 mg/kg iv at 0, 2, 6, 12, 18, and 24 weeks and were followed through week 52	Pneumonia n=4, squamous cell carcinoma n=1, epithelioid sarcoma n=1. Infusion reactions 2.3%. Other side-effects not different for placebo and infliximab groups.
Judson et al. (2008)[2]	Infliximab	To assess the efficacy of infliximab in extrapulmonary sarcoidosis, multicentre study (secondary endpoint of study Baughman et al.[1])	138 (62 combined infliximab 3 mg/kg or 5 mg/kg, 30 placebo)	Extrapulmonary organ severity was determined by a novel severity tool (ePOST) with an adjustment for the number of organs involved (ePOSTadj). The change from baseline to week 24 in ePOST as well as the improvement in ePOSTadj was greater for the combined infliximab group compared with placebo (p<0.05).	2 in infliximab 3 mg/kg group, because study drug was not received	17 extrapulmo-nary organs, among others peripheral lymph nodes, skin, bone, joints, liver, eyes	See Baughman et al.[1] No difference between groups.	3 or 5 mg/kg iv at 0, 2, 6, 12, 18, and 24 weeks and were followed through week 52	See Baughman et al.[1]

Authors	Drug	Study goal	Patients treated (n)	Outcome	Drop-outs (n)	Organ involvement	Combi/ monotherapy	Dosage	Adverse effects
Rossman et al. (2006)[3]	Infliximab	To assess the safety, tolerability and efficacy of infliximab in pulmonary sarcoidosis, multicentre study	19 (13 inflixi-mab, 6 placebo at weeks 0 and 2 and open-label infliximab for all subjects at weeks 6 and 14)	At 6 weeks the mean relative change in VC ±SD compared to baseline was 15.22 ±9.91% for infliximab and 8.39 ±3.33% for placebo (p=0.65)	None	Lungs (radiogra-phic stage II, III and IV)	-	5mg/kg iv at 0, 2, 6 and 14 weeks	Decreased WBC and elevated CK n=1, pneumonia n=1, cellulitis, acute renal failure, pulmonary embolus with consequent death n=1, and visual field defect n=1
Pariser et al. (2013)[4]	Adalimu-mab	To assess the effectiveness and safety of adalimumab in cutaneous sarcoidosis	16 (10 adalimu-mab, 6 placebo)	Improvement in target lesion area (p=0.0063), target lesion volume (p=0.0225), and Dermatology Life Quality Index score (p=0.0034); no significant changes in pulmonary function tests, radiographic findings, or laboratory studies	3 in adalimumab, 1 in placebo group. Reasons: did not receive allocation treatment, unable to be contact, unable to arrange transportation	Skin	Monotherapy	Adalimumab group 80 mg sc at week 0 and 40 mg once a week thereafter during 12 weeks, both groups 40 mg once a week during 12 weeks thereafter	Pneumonia (n=1), other adverse effects mild.

Discontinuation and polymorphism studies

Authors	Drug	Study goal	Patients followed (n)	Outcome	Predictive factors of relapse	Organ involvement	Mean duration treatment	Dosage	Combi/ monotherapy	Adverse effects
Vorselaars et al. (2013)[5]	Infliximab	To assess the relapse rate and predict relapse after discontinuation of infliximab	47	29 (62%) had relapse after infliximab discontinuation; mean follow-up time 36.6 ±22.6 months, median time to relapse 11.1 ±2.57 months	Mediastinal SUVmax scores ≥6.0 and serum sIL2R ≥4000 pg/mL at the start of therapy	Pulmonary n=30, extrapul-monary involvement n=41	8.5 ±5.8 months	5 mg/kg iv at 0, 2 and 6 weeks, and every 4 weeks thereafter	Monotherapy n=3, combination with GC n=13, immunomodulati on =19, GC/immunomodu lation n=11	Allergic reaction n=3 in patients not included
Panselinas et al. (2012)[6]	Infliximab	To assess the course of sarcoidosis after discontinua-tion of infliximab	14	12 (86%) had deteriorated as compared with their status at the time of discontinuation, mean follow-up time 12 months, 50% deteriorated within 3 months after discontinuation	-	CNS, skin	4.4 months	5 mg/kg iv at 0, 2 and 6 weeks, and every 6 weeks thereafter	Combination with GC n=7, MTX n=2, GC/MTX n=2, GC/AZA n=1, GC/cyclophospha mide n=1	Not described
Wijnen et al. (2013)[7]	Infliximab/ Adalimu-mab	To assess association *TNF-α* G-308A polymorphism and response to TNF-α inhibitors after 1 year	111 (76 inflixi-mab, 35 adalimu-mab)	83 (75%) responded well; of patients without the variant A-allele 93.6% (p<0.001) improved, while 30.3% of variant A-allele carriers improved	-	Lungs n=69, eyes n=31, SFN n=91, skin n=6, spinal cord n=1, kidney n=1	At least 1 year	Infliximab 5 mg/kg iv at 0, 2 and 6 weeks, and every 4 weeks thereafter/ Adalimumab 40 mg sc once a week	Combination with GC n=14, MTX n=29, GC/MTX n=28	Minor infections n=11, sepsis n=1, herpes zoster infection n=5, antibody formation infliximab n=9

Large case series

Authors	Drug	Patients treated (n)	Patients responding (n)	Organ involvement	Combi/ monotherapy	Dosage	Effect of therapy	Adverse effects (n)
Russell et al. (2013)[8]	Infliximab	53 organs of 42 patients	31 organs	Lungs, skin, lymph nodes, CNS	Combination with GC n=24, MTX n=20, HCQ n=23, etanercept n=1	Unknown, average treatment duration 46.2 months, up to a maximum of 85 months	Complete remission n=2; discontinuation of other therapeutic agents during infliximab n=13; symptom and clinical resolution or improvement; small improvement in FVC, FEV1, TLC (not significant)	Adverse events in 57%, discontinuation because of toxicity n=3
Hostettler et al. (2012)[9]	Infliximab	16 (treatment for 12 months)	14	Predominant pulmonary n=5, extrapul-monary n=11 (CNS, lupus pernio, heart)	Combination with GC n=6, GC/immuno-modulator n=7	3 mg/kg iv in 4/6/8 weekly intervals	Improvement of FVC 0–10% in 4/5 with predominant pulmonary involvement; complete or partial improvement in 10/11 with extrapulmonary involvement	After 4 years of therapy symptomatic bradyarrhythmia 6h after infliximab infusion, which lead to temporary discontinuation of infliximab n=1
Orum et al. (2012)[10]	Infliximab	12	12	Lungs n=9, eyes n=2, skin n=2, esophagus n=1, bone marrow n=1, kidney n=1, nose n=1	Not described	3 mg/kg iv at 0, 2 and 6 weeks, and every 8 weeks thereafter	Increase in FEV1, FVC, DLCO and TLC n=9; ACE and sIL2R in patients with raised values pretreatment decreased to values within the reference interval n=6; steroid-sparing effect on ocular sarcoidosis n=2, effect on cutaneous sarcoidosis n=2, all patients had reduced organ involvement and subjective improvement in symptoms	None

Authors	Drug	Patients treated (n)	Patients responding (n)	Organ involvement	Combi/ monotherapy	Dosage	Effect of therapy	Adverse effects (n)
Keijsers et al. (2008)[11]	Infliximab	12	11	Lungs, eyes, muscle, skin	Combination with GC n=9, MTX n=10, HCQ n=1	5 mg/kg iv at 0, 2, 6, 12, 18 and 24 weeks	ACE decreased with an average of 39% ($p<0.01$); sIL2R with 47% ($p<0.01$); VC increased with 5,4% ($p<0.01$); DLCO with 3.3% ($p<0.05$); SUVmax decreased with 55% ±35 ($p<0.01$)	Not described
Saleh et al. (2006)[12]	Infliximab	12	12	Lungs n=2, skin n=3, neurologic n=2, eyes n=1, bone n=1, liver n=1, lymph nodes n=2, hypercalcae-mia n=1	Combination with GC and/or MTX	3 mg/kg iv at weeks 2, 4, 6, 10 and 14, and every 8 weeks thereafter	All 12 patients improved significantly; lung function, skin lesions, MR imaging, CT, vision, bone scan and liver tests improved.	Mild allergic drug reaction responsive to antihistamine n=1
Doty et al. (2005)[13]	Infliximab	10	10	Lupus pernios n=5, skin non-lupus n=1, bone n=1, CNS n=1, liver n=1, muscle n=1	Combination with GC n=6, MTX n=2, HCQ n=2	5 mg/kg iv at 0, 2 and 6 weeks, and every 8 weeks thereafter	Reduction of GC dose in 5 of 6, improvement of symptoms n=9; objective improvement on physical examination, laboratory studies, or imaging studies n=10	Drug reaction n=1, oral candidiasis n=1, angioimmunoblastic lymphoma n=1
Erckens et al. (2012)[14]	Adalimu-mab	26	26	Eye (refractory posterior uveitis), lungs	Combination with oral GC n=26, MTX n=18	40 mg sc once a week	Improvement of eye disease in 22 (85%) and stabilization in 4 (15%); improvement of ACE and CRP ($p<0.01$); improvement of fatigue in 67% ($p<0.01$) and of DLCO in 88% ($p<0.01$); tapering down of GC ($p<0.01$) and MTX ($p<0.05$) after 6 and 12 months of treatment	Development of solid mass at injection side n=1, minor local skin reactions n=4

Authors	Drug	Patients treated (n)	Patients responding (n)	Organ involvement	Combi/ monotherapy	Dosage	Effect of therapy	Adverse effects (n)
Milman et al. (2012)[15]	Adalimu-mab	10	9	Intrathoracic n=9, extrathoracic n=4	Combination with GC n=8, MTX n=7, AZA n=1	40 mg sc once in 2 weeks	FDG PET uptake decreased in 9 (p=0.011) and increased in 1 patient; SUVmax fell from median 14.1 to 7.0 (p<0.03), and mean SUV fell from median 6.5 to 2.9 (p<0.02); no effect on pulmonary function tests, serum ACE and blood lymphocyte concentrations; physical component summary score of SF-36 increased (p=0.07)	Pneumonia n=1, vaginal candidiasis n=1
Banse et al. (2013)[16]	Infliximab/ Adalimu-mab	19 prescriptions in 10 patients (8 infliximab, 8 adalimumab, 3 etanercept)	14	Articular sarcoidosis involvement n=19, pulmonary n=9, ocular n=2	Monotherapy n=10, combination with MTX n=9, NSAID n=12, GC n=5	Infliximab 5 mg/kg iv per 6 weeks, adalimumab 40 mg sc once in 2 weeks, etanercept 50 mg sc once a week	At 3 months, moderate or satisfactory efficacy on DAS28 (14/19, 73.7%); after 1 year no significant effect on articular manifestations, DAS28 with ESR or CRP, global VAS score, extra-articular involvement; no impact on MTX or NSAID use; they were significant GC-sparing (prednisone 6.3 before versus 3.2 mg/day after therapy)	Mild infections n=2, toxiderma n=1 with resolution after discontinuation
Baughman et al. (2012)[17]	Infliximab/ Adalimu-mab	25 (19 infliximab, 6 adalimumab)	25 initial	Eyes	Monotherapy n=1, combination with MTX n=14, AZA n=10, LEF n=3	Infliximab 3-5 mg/kg iv at week 0, 2 and every 4 weeks thereafter, adalimumab 40 mg sc once in 1–2 weeks	Initial response to TNF-α inhibitor n=25, successful long-term therapy (ongoing treatment or remission) n=10 (7 infliximab, 3 adalimumab)	Anaphylaxis n=2, arthralgia and rash n=7, infections n=2, toxicity leading to discontinuation infliximab n=8, adalimumab n=3

Authors	Drug	Patients treated (n)	Patients responding (n)	Organ involvement	Combi/ monotherapy	Dosage	Effect of therapy	Adverse effects (n)
Elfferich et al. (2010)[18]	Infliximab / Adalimu-mab	42 (31 infliximab, 11 adalimumab)	-	Cognitive failure, fatigue	Combination with GC and/or MTX	Infliximab 5 mg/kg iv at 0, 2 and 6 weeks and every 4 weeks thereafter, adali-mumab 40 mg sc once a week	Significant higher improvement in CFQ and FAS compared to without TNF-α inhibitor (p<0.0001)	None
Baughman (2007)[19]	Infliximab / Adalimu-mab	122 (82 infliximab, 27 adalimumab, 13 etanercept)	74 (58 inflixi-mab, 13 adalimumab, 3 etanercept)	Not described	Not described	Not described	Clinical status or one or more organs improved or reduction concurrent medications	Adalimumab: infection n=2, reaction injection site n=3; infliximab: anaphylactic reaction n=2, hypotension n=2, allergic reactions n=5, gastrointestinal bleeding n=3, alopecia n=1, skin cancer n=2

ePOST, extrapulmonary physician organ severity tool, a novel severity tool to examine the state of sarcoidosis extrapulmonary organ involvement in 17 extrapulmonary organs in which each organ has to be scored on a scale from from 0 (not affected) to 6 (very severely affected); ePOSTadj score, ePOST score divided by the number of extrapulmonary organs involved; LuPGA, Lupus Pernio Physician's Global Assessment, semiquantitative rating scale representing the physician's assessment of the patient's lupus pernio status relative to baseline. ACE, angiotensin-converting enzyme; AZA, azathioprine; CFQ, cognitive failure questionnaire; CK, creatine kinase; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography, DAS28, disease activity score in 28 joints; DLCO, diffusing capacity for carbon monoxide; ESR, erythrocyte sedimentation rate; FAS, fatigue assessment scale; ^{18}F-FDG PET, fluorine18-fluorodeoxyglucose positron emission tomography; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GC, glucocorticosteroids; HCQ, hydroxychloroquine; iv, intravenous; LEF, leflunomide; MR imaging, magnetic resonance imaging, MTX, methotrexate; 6MWD, 6-minute walk distance; n, number; NSAID, nonsteroidal anti-inflammatory drug; sc, subcutaneous, SD, standard deviation; SF-36, short form-36; SFN, small fiber neuropathy; sIL2R, soluble-interleukin2-receptor; SUVmax, maximum standardized uptake value of ^{18}F-fluorodeoxyglucose positron emission tomography; TLC, total lung capacity; TNF-α, tumor necrosis factor-alpha; VAS, visual analog scale; VC, vital capacity; WBC, white blood cell.

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