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TIGHT JUNCTIONS

4. Interdisziplinäres rheumatologisches/ dermatologisches Forschungssymposium

München, 2.–3. November 2012

Abstracts

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Prof. Dr. Thomas Schwarz, Kiel

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Abstracts

1. Prognosis and outcome

1.1

Analyzing the effect of Etanercept and methotrexate on the peripheral B cell compartment in children with juvenile idiopathic arthritis

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Background. B cells have been shown to play an important role in the pathogenesis of rheumatoid arthritis and juvenile idiopathic arthritis (JIA). Current treatment strategies include methotrexate as disease-modifying antirheumatic drug and TNF- α inhibition if intensification of therapy is required. The effect of these two medications on the B cell compartment has not been investigated in depth. In adult patients with rheumatoid arthritis, one study recently demonstrated a decrease in memory B cells as a result of anti-TNF- α treatment with etanercept. However, so far no studies have been performed in patients with JIA in this respect.

Methods. We analyzed the impact of methotrexate and TNF- α inhibition with etanercept on the composition of the B cell compartment in patients with JIA. B cell subpopulations in peripheral blood were investigated by multicolor flow cytometry and immunoglobulin and BAFF serum levels determined by ELISA.

Results. More than 180 patients with JIA were included into the study. As number of B cell subpopulations in children show a strong dependency on age, age-matched groups were generated. We found a significant decrease in transitional and naïve mature B cells in patients receiving methotrexate in comparison to untreated patients and those with etanercept therapy. In addition, methotrexate resulted in significantly lower IgM and IgA serum levels. In contrast, no direct effect of Etanercept on the composition of the B cell subpopulations could be observed. However, as a more indirect effect, we found significantly lower BAFF levels in JIA patients treated with Etanercept.

Conclusion. Whereas methotrexate seems to directly impact the B cell compartment, etanercept has more an indirect effect in children with JIA.

1.2

Protein array screening reveals IGA autoantigens predicting therapy response in rheumatoid arthritis patients

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Background. One third of rheumatoid arthritis patients treated with biologicals targeting TNF- α are therapy non-responders. We investigated the differences in seroreactivity of patients responding and not

responding to TNF therapies prior and after therapy to deduce diagnostically applicable autoantigenicity patterns.

Methods. Screening with patient sera were conducted on protein microarrays consisting of 37,830 unique putative expression clones. Response patterns of different immunoglobulin classes were recorded and bioinformatically evaluated enabling us to deduce a set of proteins, which allow distinguishing between therapy responders and non-responders. Next, selected candidates were expressed recombinantly in *E. coli*, purified and further stratified with larger patient cohort by ELISA.

Results. Comparative analysis of microarray results with sera from responders and non-responders to anti-TNF drug revealed a more than 30-fold higher number of autoantigens targeted by high titers of IgA autoantibodies in non-responders compared to responders (221 vs. 6). More detailed analyses suggest that with 5 autoantigens found to be common in all individual non-responders to anti-TNF- α treatment, a reduced number of antigens might be sufficient to predict non-responsiveness. Pretreatment sera from patients with diagnosis of RA based on the ACR classification criteria who were initiated on therapy with TNF- α inhibitors were analyzed with three markers from the biomarker set of highest priority (RAB11B, PPP2R1A, KPNB1) using an ELISA's assay. In total, analyses of 69 patients were carried out, of which 13 were clearly defined as Responder and 8 were clearly defined as non-responder. Of these, already 5 (62.5%) non-responders could clearly be identified with already three markers from biomarker set of highest priority. None of the responder or intermediate responder gave any signal on said markers on IgA-level. The remaining 48 patient samples are derived prior treatment with anti-TNF- α inhibitors and were blinded. Within this set, 5 non responder patients (50%) showed clear IgA response to three markers from biomarker set of highest priority.

Conclusion. These data suggest that non-response to anti-TNF- α biologicals might be predicted based on frequency and magnitude of autoantibodies to specific IgA autoantigens. IgA-producing mucosal B cells might be important for disease persistence in TNF- α non responders.

1.3

Diagnostic potential of optical fluorescence imaging for therapy monitoring of rheumatoid arthritis

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Background and rationale. Rheumatoid arthritis (RA) is the most common joint disease among the world's population and it has been shown that early diagnosis and consecutive therapy are essential to prevent enduring disability. The introduction of immune modifying drugs like TNF-antagonists was supposed to significantly change the development of RA disease activity for individual patients and – on an epidemiological level – to reduce the impact of RA on patient's employability. However, none such effects could be detected, presumably for delayed application of the drug, insufficient identification of appropriate patient cohorts and lack of methodology to follow therapy response closely. Several studies illustrated the low predictive value of clinical versus established imaging examinations – up to 30% of patients, clas-

sified as in remission according to clinical criteria showed radiographic or ultrasound (US) disease progression. However, even the established imaging approaches may not prove ideal for therapy monitoring: while both, magnetic resonance tomography (MRI) as well as US proved capable of detecting early changes of disease activity (e.g. synovial thickness, effusion) under therapy with high sensitivity, MRI is too expensive and time consuming to be applied on a regular screening-like basis and relatively cheap US, dominating diagnostic imaging in the rheumatologic practice is strongly dependent on the experience of the observer, relatively time consuming and provides results that are difficult to compare on a longitudinal basis. Optical imaging (OI) – the visualization of light distribution in tissue for diagnostic purposes – has been applied for visualization of RA decades ago already. Contrast enhanced OI for visualization of blood vessel architecture and perfusion is also well established and a routine technique in e.g. ophthalmology. Alterations of local blood supply under pathologic circumstances and consecutive therapy-induced changes are supposed to sensitively reflect disease activity. Measurement and visualization of local perfusion with an easy, cheap and reliable method would thus be highly valuable for disease monitoring of RA and other inflammatory joint disorders. Recently, a system has been introduced for contrast enhanced OI of RA patient's hands. First studies indicate a valuable sensitivity of the approach, comparable to MRI and US but lack defined patient inclusion criteria and moreover did not evaluate the potential of OI for therapy monitoring. Purpose of this study is to assess contrast enhanced OI for visualization of anti-TNF effects on local tissue perfusion in RA patients in correlation to disease activity as reflected by established clinical scores and imaging approaches.

1.4

ICG-enhanced optical imaging for visualization of therapy response under effective TNF-inhibitor therapy in patients with juvenile idiopathic arthritis

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Background. Prognosis is different in oligo- or polyarticular involvement and influences the therapeutic strategy in patients with juvenile idiopathic arthritis (JIA). Closed to medical history and clinical examination imaging tools are useful for valid detection of inflammation. Ultrasonography and MRI are superior to clinical examination and other imaging modalities, but have practical limitations. Indocyanine green (ICG)-enhanced fluorescence optical imaging (FOI) is a novel imaging tool for visualization of inflammation in arthritis [1] and also useful in JIA patients [2]. It is a fast, easy and safe tool, which could be a valuable tool for monitoring of treatment response and remission in adults. We like to present our first experiences in using FOI for monitoring of treatment response in JIA patients.

Methods. Clinical examination (CE), laboratory tests, grey scale ultrasound (GSUS) and FOI (Xiralite, mivenion GmbH, Berlin, Germany using ICG-Pulsion®, 0,1 mg/kg/KG i.v.) of two-year-old girls with polyarticular JIA and symptoms in wrists and finger joints before (t0) and after 12 or 6 months (t1) starting with Methotrexate/Adalimumab (MA1) or Etanercept (E2) were assessed. FOI was evaluated using the FOIAS (fluorescence optical imaging activity score; [1]).

Results. At t0, clinical examination revealed increased disease activity (MA1: 10 swollen/tender joints, E2: 6 swollen/tender joints), as well as synovitis in arthrosonography (MA1). FOI displayed increased signal intensities in region of the joints (MA1 18 involved joints, FOIAS 29; E2 10 involved joints, FOIAS 14). In both cases therapy was intensive. At t1 both girls were in clinical remission without signs and symptoms in wrists or fingers (0 tender/swollen joints). Furthermore, FOI showed a

significant decrease of inflammatory activity (MA1: 0 involved joints, FOIAS 0; E2: 1 involved joint, FOIAS 1).

Conclusions. The increase of the therapeutic armamentarium in paediatric rheumatology permitted to define new treatment targets in JIA. Inactive disease or remission is achievable. The target is not easy to define. If the clinical evaluation of subclinical activity in inflammatory rheumatic disease is inferior to imaging modalities, a valid method for detection of residual subclinical inflammatory activity would be highly welcomed. With current knowledge, FOI seems to be an interesting option. The clinical decrease of symptoms correlates in the reported JIA patients with the decrease of pathological findings in FOI. The structured evaluation of FOI for the scientific status in JIA is ongoing.

1. Werner SG, Langer HE*, Ohrndorf S*, Bahner M, Schott P, Schwenke C, Schirner M, Bastian H, Lind-Albrecht G, Kurtz B, Burmester GR, Backhaus M. *equal contribution (2012) Inflammation assessment in patients with arthritis using a novel in vivo fluorescence optical imaging technology. *Ann Rheum Dis* 71(4):504–10
2. Werner SG, Langer HE, Horneff G (2012) Fluorescence optical imaging of juvenile arthritis. *J Rheumatol* 38:1447

1.5

Role of developmental endothelial locus (Del)-1 in arthritis

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Background. Rheumatoid arthritis (RA) is a highly prevalent chronic inflammatory disease that mainly targets the synovial membrane, cartilage and adjacent bone. Various immune cells are found in the inflamed synovium that produce a broad range of cytokines that maintain chronic synovitis and drive joint destruction. In the past decades, numerous studies have focused on proinflammatory factors involved in the pathogenesis of RA, however, knowledge is limited on negative regulators of inflammation. In our previous studies, we have recently identified a novel anti-inflammatory factor, developmental endothelial locus-1 (Del-1; also known as EDIL3), that negatively regulates the inflammatory process in periodontitis by suppressing LFA-1-dependent neutrophil adhesion and IL-17 production.

Methods. In the current project, we will determine whether Del-1 regulates the disease course of arthritis in mice and whether Del-1 is downregulated in patients with RA. To test our hypothesis we will assess the following aims: (I) determine the expression and cellular source of Del-1 in healthy and arthritic mouse joints, (II) investigate the role of Del-1 in a mouse arthritis model, and (III) assess Del-1 levels in serum and synovial tissue from RA patients.

Conclusion. A better understanding of the role of Del-1 in the pathogenesis of arthritis may lead to the development of novel targeted therapies to treat patients with RA.

1.6

A 1-year observational study of the use of Etanercept in routine German clinical practice to treat patients with psoriasis arthritis by rheumatologists and dermatologists: interim analysis

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Background. RCTs are important and powerful tools in assessing efficacy and safety but have their limitations in terms of generalisability.

In order to assess safety and efficacy of Etanercept, there is a need of performing observational studies of unselected patients. Also treatment strategies between rheumatologists and dermatologists can be compared.

Methods. The study aims to provide a holistic assessment of patients receiving Etanercept in a real world setting. This will include centers that would not normally take part in RCT. The study will assess treatment with Etanercept with descriptive statistics of the parameters safety and effectivity. The results shown here are an interim analysis of the entire study.

Results. 1313 patients in 294 centres were evaluated for 52 weeks in the entire time period of November 2005 until March 2012. 143 patients were treated by dermatologists, 1170 by rheumatologists. The mean age was 51 ± 12 years (54.5% female), the mean disease duration 7 ± 8 years and the mean number of previous DMARDs 2.2 ± 1.3 . The initial dose was predominantly 1×50 mg/w (56.4%) or 2×25 mg/w (27.6%). 1242 patients were pretreated with MTX.

Effectivity. The DAS28 decreased from 4.8 ± 1.4 to 3.1 ± 1.4 in week 12 and 2.7 ± 1.4 in week 52. In week 12 75.6 % reached a good to moderate EULAR-response (week 52: 85.2 %), and 37.7 % a DAS remission (week 52: 53.8%). The PASI decreased from 15.3 ± 12.8 to 6.8 ± 8.1 (3.4 ± 5.3 in week 52). The BSA decreased from $11.5 \pm 17.6\%$ to 6.3 ± 11.6 in week 12 and $3.9 \pm 7.5\%$ in week 52.

Safety. The incidence rates for UEs and SUEs possibly related to Etanercept were 35.6% and 2.1% respectively. No deaths were reported.

2. Answers to clinical questions

2.1

A new measure for tight control?! – Detection of early central changes in rheumatoid arthritis patients by functional MRI and its correlation to the neurohormonal axis

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Background. In rheumatoid arthritis (RA) cytokine dysregulation with a misbalance between pro-inflammatory and anti-inflammatory cytokines is central to the pathogenesis. From a subclinical situation, breach of tolerance leads to subsequent inflammation and articular destruction [1]. A central key cytokine to this process is tumour necrosis factor alpha (TNF- α) based on preclinical data and clinical targeting. Targeting TNF- α delivers beneficial effects on joint damage and function as well as disease outcome, but also on tissue inflammation and cell infiltration measured histologically in biopsies as part of proof of concept studies. However, TNF- α blockade is effective in only approximately 75% of patients receiving treatment, thus leaving room for improvement and rendering it necessary to explore the pathways and mechanisms to identify therapy responders from non-responders [2].

Methods. This single arm, single blinded, mono center trial will recruit 12 patients with rheumatoid arthritis qualifying for a treatment with TNF- α inhibition according to local health guidelines. Patients will be blinded to a dummy injection on day 0 with a subsequent switch to TNF- α inhibitor Etanercept on day 7 for all patients. Dummy injection will be sterile aqua ad injectabile (same volume as Etanercept). Etanercept will be administered according to SmcP 50 mg s.c. every week.

Results. Primary end point: Difference on fMRI assessment control injection vs. anti-TNF therapy. 1 day post injection. Secondary endpoint: Changes in pain, SF-36 and HAQ compared to the fMRI assessment. Changes in the neuro-hormonal axis in correlation to the fMRI assessment. Correlation of DAS28 responders (day 28) with fMRI assessment (day 1).

Conclusion. With this study we first want to confirm our findings in earlier studies [3] where we have seen a very early decrease in activity by fMRI after TNF- α blockade, suggest that TNF- α might act with a fast response via the root ganglions expressing TNF receptors [4] with subsequent effects on peripheral pain with later amelioration of peripheral synovitis. The second important thing is if the suggestion by Atzeni et al. that anti-TNF- α may also support anti-inflammatory pathways, such as the hormonal axes [5] can be seen.

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2.2

Development and validation of a specific rheumatic gait analysis

F. Kreuzpointner

Abstract not submitted at time of publication

2.3

A xenograft model for human psoriasis

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We established a xeno-transplantation model using healthy human skin transplanted to NOD.Cg-Prkdcscid IL2RgtmWjl/SzJ (NOD-Scid gamma-chain-/-) mice lacking T cells, B cells and NK cells to create a human mouse model for psoriasis. During the first two weeks post transplantation of healthy human skin, a scab formed and the xenograft shrank in size. After 6 to 8 weeks, the skin had started to heal and vascularization was visible from beneath the transplant. In order to document any histological changes during the engraftment, we examined skin transplants at various time points after transplantation. Prior to its transplantation, the skin exhibited CD1a and CD207/Langerin-positive Langerhans cells (LCs) as well as dermal CD11c-positive dendritic cells (DCs) and CD68-positive macrophages. We demonstrated that xenografting leads to a transient loss of epidermal Langerhans cells, which re-established in the epidermis of the xenografts 6–9 weeks after transplantation. By staining of Ki-67 expression, we found a markedly increased proliferative activity among repopulating LCs. This finding supports the hypothesis of a local LC-reconstituting population independent of blood precursors. In our current study we intend to establish a model for in vivo analysis of psoriasis by human PBMC transfer into NOD-Scid (lacking T and B cells) and NOD-Scid gamma-chain-/- mice (as described above). For this purpose we have transplanted non-lesional and lesional skin from psoriatic patients. After 10 weeks human skin biopsies were obtained and histologically

examined. $1-3 \times 10^6$ PBMC from psoriatic patients (skin donors) were activated by the presence of IL-2 and SEB and transferred intradermally into immunodeficient mice, 12 weeks after they had received a xenotransplant of human skin. All mice were clinically observed and digitally documented. We were able to detect in some human transplants histological changes of psoriatic-like lesions. In summary, this serves as a model for the investigation of psoriasis under experimental conditions, in particular, to examine dermal and epidermal dendritic cells and to determine their role in the development of psoriasis, in both presence and absence of human T cells.

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2.4

The way to live with axial spondyloarthritis: patients are using different coping strategies

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Background. The main symptom of patients with axial spondyloarthritis (axSpA) has been traditionally evaluated from a biomedical perspective but coping strategies may also have an important role in patients' adjustment to back pain. The objective was to examine differences in coping strategies in patients with axSpA in a 6-month longitudinal study.

Methods. A total of 100 consecutive patients diagnosed with axSpA according to the ASAS classification criteria including patients with ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA) completed clinical and psychological assessments at baseline and after 6 months. The vast majority of patients (>90%) was treated with non-steroidal anti-inflammatory drugs (NSAIDs). Standardized clinical assessment tools evaluated pain (numerical rating scale), disease activity (BASDAI, ASDAS), physical functioning (BASFI), coping strategy (Trier scale for coping), quality of life (QoL; ASQoL), health status (SF-36) and patient acceptable symptom state (PASS).

Results. AS was diagnosed in 56 and nr-axSpA in 44 patients, 92 patients completes follow-up. While 55.6% of the patients did not seem to have a preferred strategy to cope with the disease (which does not mean that they have not used coping strategies, it just means that they have not preferred one) the remaining patients preferred the following strategies at baseline: spiritual resources (12%), rumination (10.8%), information seeking (9.7%), withdrawal from society (3.3%), social embedding (2.2%) and fight back (2.2%). At baseline, 38% rated their disease status as acceptable (PASS+). Patients who preferred the strategy rumination rated their disease status as not acceptable (PASS-) in 88.9%. In contrast, rumination was only used in 2.9% by PASS+ patients. The proportion of PASS+ patients did not change much at follow-up and most patients had not changed their coping strategy. The PASS+ patients reported to use the strategy social embedding more often at follow up (25.7%) as compared to baseline (11.4%). Furthermore, this strategy was more often used by the PASS+ vs. the PASS- patients at follow up (25.7% vs. 7%, $p < 0.001$), respectively. A change in strategy was only reported by 7.6% of the patients with no preferred strategy at baseline (mostly to information seeking). Regarding coping there were no major differences between patients with AS and nraxSpA.

Conclusions. Most patients with axial SpA did not use a preferred coping strategy. Our findings suggest that negative emotion focused coping styles (e.g. rumination) was associated with non-acceptance of the

current health status. Whereas, active coping styles (e.g. social embedding) seems to have a positive influence on disease acceptance.

2.5

A part of the lupus susceptibility gene loci sle2 including c-mpl regulates terminal plasma cell differentiation in murine lupus

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Background. Systemic lupus erythematosus (SLE) is a polygenic autoimmune disease characterised by B cell hyperactivity and hypergammaglobulinemia. Also, it had been reported that a considerable fraction of SLE patients exhibits increased megakaryocytes (MKs). Previously, we showed that MKs support plasma cell generation and survival in bone marrow niches by providing IL-6. Accordingly, c-mpl KO mice, deficient for the receptor for thrombopoietin which is the major regulator of megakaryopoiesis, also exhibit deficiencies in the generation of mature plasma cells in bone marrow. BcN mice contain the three sle loci sel 1–3 on C57BL/6 (B6) background and spontaneously develop a lupus-like disease. Gene products encoded on sle1–3 lead to an increase in plasma cell numbers in spleen resulting in hypergammaglobulinemia. Interestingly, these mice also exhibit extramedullary megakaryopoiesis in the spleen, most likely due to a point mutation in c-mpl which is located at the edge of the sle2 locus. Based on this, we hypothesise that increased megakaryopoiesis and the c-mpl/TPO pathway contribute to the abnormally increase of plasma cells in SLE.

Methods. To test our hypothesis, we generate BcN.c-mpl-/- mice by crossing BcN and B6.c-mpl-/- mice. Meanwhile polymerase chain reaction (PCR) and microsatellite technology were used for genotyping. Megakaryocytes and plasma cells are measured by flow cytometry.

Results. Currently mice are generated that carry the complete sle1 and sle2 loci and most of sle2, except c-mpl gene together with a locus coding for about additional 20 proteins. In these mice, populations of splenic megakaryocytes and mature plasma cells, but not B cells or plasma cell precursors, significantly decreased compared with BcN.c-mpl+/+ and BcN.cmpl+/- mice. These results indicate that c-mpl (or other genes missing in the current mouse model) is crucial in the regulation of terminal plasma cell differentiation.

Conclusions. In accordance with our original hypothesis, the deletion of c-mpl gene together with genes encoding for a few other proteins on sle2 led to a drastic reduction in the size of the plasma cell and megakaryocyte compartment. However, to prove this hypothesis we need to continue breeding to generate mice containing all sle1–3 genes except c-mpl. If our hypothesis turns out to be wrong, alternatively, backcrossing could also identify other genes mapping on sle2 locus that regulate terminal differentiation of plasma cells in this lupus model.

2.6

Targeting the cutaneous microenvironment: clinical impact of the cytokine network in chronic inflammatory skin diseases – project outline

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T cell-mediated skin diseases such as atopic eczema and psoriasis represent a most challenging field of molecular medicine. Pioneer clinical studies proofed that application of biologic drugs (Enbrel, Remicade) is a revolutionary and highly promising approach for treatment of im-

mune-mediated skin diseases. Increasing knowledge on the outcome of a T cell response in the disease-specific microenvironment opens new horizons for more specific and more effective biologic treatments. A number of recent studies, however, demonstrate that a combination of rather than single cytokines exert the full impact of T cells on keratinocytes. Synergisms and antagonisms of IL-17, IL-22 with IFN- γ , IL-4 and TNF- α have been described recently. These findings underline that preclinical and clinical studies on the effectiveness of newly developed drugs are insufficient when investigating isolated cytokine effects, but they must imply the disease-specific microenvironment. The aim of this study is to analyze single and synergistic effects of T cell cytokines on primary human keratinocytes and investigate the potency of single and combinatorial biologic drugs for clinical application in atopic eczema and psoriasis. To achieve this aim, in vitro models that closely resemble the in vivo situation will be used. Effects of single cytokines and key cytokine combinations as drug target for atopic eczema and psoriasis will be investigated in a three-step experimental approach: 1. effects of skin-derived T cell supernatant on human primary healthy and disease keratinocytes. Modulation of effects by neutralizing key T cell cytokines/cytokine combinations. 2. Verification on larger scale and identification of single T cell subset contribution to disease using skin-derived T cell clone supernatant on keratinocytes. 3. In vivo-like proof of concept: effects of blister fluid obtained from lesional skin on keratinocytes. Blisters will be induced mechanically over lesional skin of atopic eczema and psoriasis patients using the method of suction blister. In that way, the in vivo concentration and combination of cytokines in the microenvironment can be extracted and used for single experiments. This study will give deeper insights into the action of single cytokines in a disease-specific microenvironment and build the basis for applying the most appropriate therapy to inflammatory diseases of the skin.

2.7

Analysis of the immunoregulatory potential of human B cells in systemic lupus erythematosus

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Background. Maintenance of immune tolerance depends on regulatory mechanisms, among which regulatory T-cells (Treg) are considered to be crucially important. Previously B cells with immunoregulatory properties have been found in mice (Breg) but their role in humans is ill defined. Our lab has recently identified activated human B cells with regulatory properties (induced Breg, iBreg) in vitro, which could induce temporary anergy and apoptosis in a subpopulation of Th cells upon polyclonal stimulation. Our next aim was to define the role of regulatory B cells in autoimmune disease, such as systemic lupus erythematosus (SLE). Since Treg defects are reported, at least in advanced stages of this disease, it could be suspected that Breg might be affected, as well.

Methods. Highly purified CD19+B-cells and CD4+Th-cells were separated from PBMC of healthy donors (ND) and SLE patients by MACS-sorting. B cells were prestimulated via their B cell receptor (BCR) with anti-IgM/ IgG or SAC (Staphylococcus Aureus Cowan I Antigen) for 3 d and sorted into highly activated FSChi (B+) and small resting FS-Clo (B-) B cells by FACS-sorting. Upon 4d coculture with Th cells and α CD3+IL-2, T cell proliferation was determined by 3H-TdR incorporation.

Results. SLE-B+ exhibited a significantly diminished suppressive activity towards ND-Th cells in contrast to ND-B+ (T cell proliferation in presence of SLEB cells 52% of proliferation of T cells alone vs. less than 35% in presence of ND B cells, n=38). Similar effects were noted when SLE-T cells were used instead of ND-T cells, confirming that SLE-T cells were equally susceptible to iBreg signals and that SLE-B

cell defects were independent of T cell origin. Cell viability and expression of candidate activation markers, such as CD25, CD80, B7-H1, CD27 or the cytokines IL6, TNF- α and IL-10 were comparable between both B-cell populations, confirming that differences in activation or differentiation state might not be responsible for defects. Increasing the SLE-B cell number reinforced the suppressive effects, however could not fully reach the suppressive level of ND B cells. B cells from patients with another systemic autoimmune disease, granulomatosis with polyangiitis (formerly Wegener's granulomatosis) exhibited no regulatory defects in our system, suggesting that observed iBreg defects were specific for SLE and not a general sign for inflammation or autoimmunity.

Conclusions. iBreg from SLE patients are less effective in control of T-helper-cells in vitro, which might contribute to pathogenesis or progression of this systemic autoimmune disease.

2.8

Identification of very early PSA joint alterations

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Abstract not submitted at time of publication

3. Clinical trials

3.1

A 1-year observational study of the use of Etanercept in routine German clinical practice to treat rheumatoid arthritis patients: a health economic, safety and effectiveness evaluation

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Background. The diagnosis, evaluation and treatment of RA continue to undergo rapid change. Randomized controlled trials such as the TEMPO study have demonstrated the efficacy and safety of the combination of Etanercept and methotrexate. Importantly the TEMPO study showed that patients treated with Etanercept and methotrexate could reach the newer therapeutic goals of low disease activity and remission and that the physicians, patients and payers are no longer prepared to accept the goal of "Reduction of symptoms". RCT are important and powerful tools in assessing efficacy and safety but have their limitations in terms of generalisability. In order to assess health economics, clinical effectiveness and safety of Etanercept, there is a need of performing observational studies of unselected patients.

Methods. The study aims to provide a holistic assessment of patients receiving Etanercept in a real world setting. This will include centers that would not normally take part in RCT. The study will assess treatment with Etanercept with descriptive statistics of the parameters health economics, safety and effectiveness. The results shown here are an interim analysis of the entire study.

Results. 4449 patients in 315 centres were evaluated for 52 weeks in the entire time period of October 2006 until March 2012. The mean age was 56 $\pm$ 13 years (75% female), the mean disease duration 10 $\pm$ 10 years and the mean number of previous DMARDs 2.8 $\pm$ 1.3.

Effectivity. The DAS28 decreased from 5.4 $\pm$ 1.3 to 3.8 $\pm$ 1.5 in week 12 and 3.3 $\pm$ 1.4 in week 52. In week 12, 67.0% reached a good to moderate EULAR-response (week 52: 79.6%), and 22.5% a DAS remission (week 52: 34.1%). The mean morning stiffness decreased from 60 to 15 min in week 12 (week 52: 10 min). Also the parameters disease activity,

pain and fatigue (all measured by VAS) decreased continuously over time.

Safety. The incidence rates for UEs, SUEs and SUE with possibly related to Etanercept were 44.8%, 12.8% and 2.8% resp. 21 deaths were reported (0.5%).

Health economics. The FFbH Score increased from 61.1 ± 23.1 before treatment to 68.9 ± 23.1 in week 12 and 71.2 ± 23.0 in week 52. 35.9% (40.9) of the patients reached FFbH remission in week 12 (week 52). Also the WPAI:SHP decreased continuously over time; e.g. the percentage of work time missed due to RA decreased from 23.0 ± 37.4 to 14.2 ± 31.3 in week 12 and 12.4 ± 28.7 in week 52.

3.2

Immunoregulatory function of Etanercept in psoriasis at the level of pro-inflammatory slan (6-sulfo LacNAc) expressing dendritic cells

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Dermal dendritic cells (DCs) play a central role in the immunopathology of psoriasis. We previously identified slanDCs as proinflammatory DCs in human blood and as an inflammatory dermal DC subset in psoriasis. SlanDCs stand out by their capacity to produce high levels of TNF- α , IL-6, IL-1 β , IL-23 and IL-12 and program strong Th1/Th17 T cell responses. Here we asked for the effects of TNF- α inhibition by Etanercept on inflammatory slanDCs in skin and blood of patients with psoriasis. We studied slanDCs in skin and in blood of 10 patients with psoriasis before and during 24 weeks of treatment with Etanercept. Increased numbers of slanDCs in psoriatic lesions were ameliorated by Etanercept to the level of healthy skin after 24 weeks. In parallel we observed a reduction in the numbers of TNF- α -, IL-23p19- and CD11c-expressing cells in psoriatic skin. In contrast to this overall inhibitory effect of Etanercept on markers of inflammation, the TNF- α and IL-23p19 expression among lesional slanDCs remained constant. Notably the percentage of slanDCs among all dermal IL-23p19 positive cells increased during treatment with Etanercept. This indicated that slanDCs still present in skin lesions after Etanercept treatment retained their expression of IL-23 and TNF- α , suggesting that a stimulatory circuit for the activation of these pro-inflammatory dermal DCs remained active. This was supported by the lack of significant costaining of slanDCs and the marker of apoptosis caspase 3 whereas CD163+ macrophages were stained positive for caspase 3 after Etanercept treatment. In addition, with therapy the percentage of slanDCs in blood increased 3.8-fold, while their HLA-DR expression was reduced. In vitro Etanercept efficiently reduced the capacity of blood derived slanDCs to produce IL-1 β , IL-6, IL-23 and IL-12p70. This study for the first time documents the immunomodulatory potential of Etanercept on a distinct and highly pro-inflammatory population of DCs in skin and blood.

3.3

Similar response rates in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis after one year of treatment with Etanercept – results from the ESTHER trial

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Objective. We assessed whether there is a difference to Etanercept (ETA) treatment in patients with ankylosing spondylitis (AS) compared to non-radiographic axial SpA (nr-axSpA) patients with a disease duration of <5 years.

Methods. AS (n=20) and nr-axSpA (n=20) patients who were treated with ETA for one year were compared for differences in baseline data and treatment effect. Clinical, laboratory and magnetic resonance imaging of sacroiliac joints (SI-joints) and spine were analysed.

Results. At baseline there were no significant differences between the 20 AS and the 20 nr-ax SpA patients regarding age, disease duration, gender, HLA-B27 and clinical disease activity in terms of BASDAI, CRP, and MRI SI-joint and spine scores in the AS compared to the nr-ax SpA group. After one year of treatment with ETA the treatment effect was similarly good in AS and nr-ax SpA [reduction of BASDAI by 3.3 (95% CI 2.2–3.8) vs. 3.6 (95% CI 2.8–4.4) and reduction of ASDAS by 1.8 (95% CI 1.5–2.2) vs. 1.8 (95% CI 1.5–2.1), respectively].

Conclusions. The response rate to TNF blockers does not differ between AS and nr-ax SpA if the baseline data regarding symptom duration and disease activity are similar for the two groups.

3.4

OMERACT 11 Meeting 2012

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Background. Beim diesjährigen OMERACT-11-Treffen in Pinehurst, North Carolina, USA wurde die bisherige Arbeitsweise des OMERACT-Prozesses einer Revision und Neustrukturierung unterzogen. Der bisher verwendete OMERACT Filter „Truth, Discrimination and Feasibility“ wurde überarbeitet. Die OMERACT-RA-Flare-Gruppe besteht seit 2008 [1]. Sie stellte nunmehr ihre Forschungsergebnisse zu „Schüben bei Rheumatoider Arthritis“ („Flare“) in einem Workshop vor.

Methoden. Für die rheumatoide Arthritis (RA) gibt es derzeit keinen Konsens hinsichtlich der Definition eines „Schubes“. Ziel der Arbeitsgruppe ist es, in Zusammenarbeit mit Patienten eine auf Daten beruhende, konsensbasierte Definition eines rheumatischen Schubes, sowie geeignete Messinstrumente zu entwickeln und zu validieren. Im Fokus stehen hierfür klinische Studien und Langzeitbeobachtungsstudien [2, 3].

Ergebnisse. Schübe sind ein integraler Bestandteil der Krankheit der meisten RA-Patienten. Die Natur der Schübe variiert in Intensität, Ausprägung, Symptomen, Dauer, Frequenz und Folgen für den Patienten. Schübe sind in der Regel nicht vorhersehbar und führen zu einer Beeinträchtigung des Patienten. Das Ausmaß der Beeinträchtigung durch die Schübe wird durch individuelle Begleitumstände der Lebenssituation, durch Bewältigungsstrategien und das jeweilige Setting, in dem diese eingesetzt werden, determiniert. Die Kriterien zur Definition eines Rheumaschubes müssen sowohl die Perspektiven des Patienten, als auch des Arztes reflektieren. Ein Schub resultiert im

Extremfall in einer derartigen Krankheitsverschlechterung, dass eine Therapieumstellung erforderlich wird.

Schlussfolgerung. Es ist notwendig, Messmethoden zur Erfassung von Schüben zu entwickeln, um antirheumatische Therapien zu optimieren. Hierfür ist es wichtig, die Dauer eines Schubes und die Zeit zwischen einzelnen Schüben zu erfassen sowie Dosisanpassungen vorzunehmen oder ein Absetzen der Therapie durchzuführen, wenn eine Remission erzielt worden ist.

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3.5

Tofacitinib (CP-690,550), an oral Janus Kinase inhibitor: pooled phase 3 analysis in a German rheumatoid arthritis study population

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Aim. Tofacitinib (CP-690,550) is a novel, oral JAK inhibitor investigated as a targeted immunomodulator and DMARD for rheumatoid arthritis (RA). This analysis across phase 3 RA studies assesses tofacitinib in the German subpopulation.

Method. German patients receiving tofacitinib 5/10 mg twice daily (BID) or placebo in combination with MTX or other nonbiologic DMARD(s) in 4 phase 3 studies (≥6 months) [Studies in MTX IR NCT00847613/ NCT00853385, DMARD IR NCT00856544, anti-TNF IR NCT00960440] were pooled. Disease activity including ACR20 response, DAS28-4(ESR) <2.6 and functional status by HAQ-DI score and safety was assessed.

Results. Most subjects were female (78%) and age range was 20–79 years. At baseline (n=188), mean HAQ-DI score ranged from 1.3–1.6. RF and anti-CCP positivity ranged from 52–65% and from 45–74% respectively. At 6 months, ACR20 response and DAS28-4(ESR) <2.6 rates in tofacitinib 5mg/10mg BID were 56%/69% and 13%/22% respectively. 6 month mean change from baseline in HAQ-DI was –0.4 in tofacitinib 5 mg/10 mg BID. AEs were reported for tofacitinib 5 mg/10 mg as 32%/58% and 33%/39% for month 0–3 and 3–6 respectively. Infections represented the most frequent reported AEs. A total of 9 discontinuations due to AE and 13 SAEs occurred over the study duration.

Conclusions. Tofacitinib has demonstrated efficacy in reducing signs and symptoms and improving physical function in a German subpopulation of RA patients. The safety signals detected in this analysis were consistent with those in the global tofacitinib RA development program.

4. From nano to macro

4.1

Remission induction by Etanercept in enthesitis-related arthritis JIA patients (juvenile undifferentiated spondylarthropathy) – REMINDER Study

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Background. According to the mutually accepted ILAR classification enthesitis-related arthritis is a juvenile idiopathic arthritis category, clinically related to the syndrome of undifferentiated spondyloarthropathy in adults. This study is intended to generate first evidence that treatment with Etanercept is safe and effective in patients diagnosed with ERA-JIA who are able to acquire stable remission (inactive disease). Furthermore the stability of remission off medication in patients treated with Etanercept will be demonstrated.

Methods. This is a multi-center, open-labeled uncontrolled study of 24 weeks, followed by randomized, double-blind, placebo-controlled, withdrawal, parallel group treatment phase of further 24 weeks. In phase 1, a total of 40 patients with ERA-JIA will be treated with Etanercept (0.8 mg/Kg up to a max of 50 mg sc per week) for 24 weeks. Patients who demonstrated at least a PedACR30 response in phase 2 will be randomised to two groups. Group 1 will continue treatment with Etanercept for a maximum of further 24 weeks. Group 2 will receive placebo and will be followed up to observe the duration of a remission without therapy. The study phase 2 is terminated in case of a disease flare or after 24 weeks, whichever occurs earlier. Patients who flare in will enter phase 3, an open label extension phase. Patients who do not flare until week 48 will terminate the study.

Results. The study is ongoing. 26 patients have been recruited so far. 17 patients have reached week 24, 15 patients (88%) exhibited no tender joint, 16 patients (94%) no swollen joint, 15 patients (88%) no active joint, 16 patients (94%) showed a physician global indicating no disease activity, 17 patients (100%) had a normal ESR (<20 mm/h), 17 patients (100%) had a normal CRP (<5 mg/l), 15 patients (88%) had no tender enthesitis points. "Inactive disease" could be documented in 14/17 patients (82%), 1 patient did not reach ACR30 at week 24 and was not randomized. 16 patients were randomized to receive placebo or Etanercept, 4 flares occurred, 2 at week 28 and 2 at week 32, 8 patients reached week 48 without a flare. So far 50 adverse events have been observed, 6 cases with gastroenteritis, 6 with headache, 3 with upper airway infection, all other occurred once only. 1 serious adverse event, a posttraumatic renal hemorrhage, judges as not related to study drug was documented.

Conclusion. In this ongoing study Etanercept proved to be an effective therapeutic approach for patients with enthesitis-related arthritis (ERA-JIA) with a high rate of responders and a high rate of patients reaching "inactive disease" after 24 weeks of treatment. Since the study is still recruiting and blinded all results are preliminary. There was no new safety information.

4.2

Synovial inflammation determined by 3 Tesla magnetic resonance imaging in patients with rheumatoid arthritis treated with Etanercept

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Background. Conventional disease-modifying anti-rheumatic drug (cDMARD) treatment is insufficient in some patients with rheumatoid arthritis (RA) thus requiring antagonists for tumor necrosis factor alpha. Treatment with these agents demonstrates excellent remission rates that have been documented with conventional radiographs and some magnetic resonance imaging (MRI) studies. The latter method has the advantage of showing early inflammatory changes or flares as compared to conventional radiographs, and the 3 Tesla technique allows higher spatial resolution as compared to 1.5 Tesla analysis. Especially early and thus prognostically relevant subchondral bone lesions might be detected more precisely.

Method. Ongoing epidemiologic clinical pilot MRI study with 10 ACR/EULAR-positive, RA patients with inadequate response to two cDMARDs and thus an indication for Etanercept using the rheumatoid arthritis magnetic resonance imaging system (RAMRIS). These patients are compared to 10 patients adequately responding to cDMARDs. 3 Tesla MRI (PDSPAIR; T₁ with and without contrast agent) using a multi-channel hand coil are performed at baseline, after four months, and after 12 months. MRI analyses include RAMRIS scoring with examination for synovitis, effusion, subchondral erosion, and also bone marrow edema. Data are compared to and correlated with CRP and clinical parameters (DAS28, HAQ, VAS).

Results. Up to date, 9 patients of the Etanercept arm were included. Data at baseline, after four months and after 12 months are available for four patients. The mean (±SD) RAMRIS score changed from 28.8±4.9 to 24.75±6.6 after one year. Separate examination for synovitis showed a decrease from 5±1.5 to 3.5±2.2 whereas subchondral bone erosion and bone marrow edema did not change after 12 months. In contrast, additional findings such as VAS and daily doses of prednisone decreased in all four patients. The DAS28 decreased in two patients after 12 months below 2.8. Four patients adequately responding to cDMARDs (methotrexate) were also included thus far. Data at baseline and after 12 months are available for one patient: RAMRIS/DAS28 at baseline and after 12 months were 17.0/1.39 and 17.0/1.84, respectively. The mean RAMRIS of four patients at baseline was 13.5±4.9.

Conclusions. The results indicate partial remission after 12 months of treatment with Etanercept. More patients, data after 12 months and statistical analysis are required to document solid remission rates. In addition, further serological markers will be examined.

4.3

Topoproteom-Analyse der Psoriasis unter Behandlung mit Etanercept

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Hintergrund und Methoden. Sechs Patienten mit einer schweren chronisch aktiven Psoriasis wurden mit Etanercept (Enbrel®) in einer Dosierung von 2×50 mg s.c. pro Woche über 12 Wochen im Rahmen einer Investigator-initiierten Studie (EudraCT-Nr: 2008-006227-31, IDEA-Studie) behandelt. Dabei wurden 6 mm große Stanzbiopate aus befallener und unbefallener Haut unmittelbar vor Therapiebeginn und aus ursprünglich befallener Haut zu den Zeitpunkten

Woche 6 und Woche 12 für eine Topoproteom(TPX)-Analyse gewonnen.

Ergebnisse. Die Verträglichkeit der Therapie war sehr gut. Bei Baseline lag der PASI im Mittelwert bei 21,6 (Spanne von 15,9–31,4). Initial betrug im Mittel der DLQI auf der 30-Punkte-Skala von Finlay & Kahn 14,7 (1–26) und der Pruritus auf einer 10-Punkte-VAS 5,2 (0–10). Nach 12-wöchiger Behandlung mit Etanercept zeigte sich eine substantielle Therapiewirksamkeit mit einem Abfall des PASI auf einen Mittelwert von 5,8 (2,7–9,6), entsprechend einer summarischen PASI-Respons von 71,2%. Entsprechend kam es im Mittel zu einer Besserung des DLQI auf 4,2 (1–17) und des Pruritus auf 1,7 (0–5). Die Hautbiopate sind Gegenstand einer TPX-Analyse. Dabei wurde eine breite Antikörper/Binder-Bibliothek etabliert, welche die folgenden Epitope detektiert: Aktin, BCL2, c-myc, CCR6, CD11a, CD11b, CD120a, CD120b, CD138, CD15, CD1a, CD2, CD207, CD24, CD28, CD29, CD3, CD31, CD4, CD44, CD45, CD45RA, CD45RO, CD52, CD54, CD56, CD58, CD62E, CD62P, CD68, CD7, CD8, CLA, Kollagen Typ IV, Cytokeratin 14, FactorXIII Subunit A, HLA-DR, IL-22R, IL-23R, Ki67, Podoplanin, Propidiumjodid-Bindungsstelle, SNA1, STAT3, TIA1 und Vimentin. Im Vergleich der befallenen Haut vor Therapiebeginn mit der ursprünglich befallenen Haut nach 12 Wochen Therapie zeigte sich ein signifikanter Abfall für die Expression der Einzelpeptide CD45, CD45Ro, CLA, CD11a, CD138, CD15, c-myc und STAT3. Auf kombinatorischer Ebene der Analyse fanden sich für die Expression der TPX-Signatur CD2+/CD3+/CD4+/CD45+/CD45Ro+ signifikante Effekte im Vergleich von unbefallener Haut vor Therapie (184±266 PEN = „pixel events normalized“), befallener Haut vor Therapie (6816±4133 PEN) und ursprünglich befallener Haut nach 12 Wochen Therapie (2298±3340 PEN). Aus der Vielzahl der Ergebnisse der Studie lässt sich hier also exemplarisch die klinische antipsoriasis-Wirksamkeit von Etanercept mit der Suppression einer distinkten T-Zell-Subpopulation vom Memory-Phänotyp als ein relevantes Major-Target korrelieren.

4.4

Analysis of the spondylitis-ankylosis sequence and effects of Etanercept treatment in a murine model of spondyloarthritis using high-resolution magnetic resonance imaging and immunohistochemistry

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Background. Ankylosing spondylitis (AS) is an immune-mediated inflammatory disease that affects the axial skeleton but also peripheral joints leading to structural and functional impairments, thus to a severe decrease in the quality of life. Inflammation of the spine in patients with AS is not accessible to routine biopsies. Hence, the knowledge of histopathology in AS originates from a few studies that used tissue specimens obtained from surgical interventions of the hips or the spine. TNF-α was overexpressed in tissue specimens from the sacroiliac joints, providing a strong rationale for the use of TNF-inhibitors (TNFi).

Scientific rationale. Evidence suggests a link between inflammation and new bone formation. Magnetic resonance imaging (MRI) research revealed that fatty bone marrow lesions occur when inflammation resolves and that they precede ankylosis. Whether TNFi influence any of these sequences is still unclear and subject of current discussions. Clinical studies that tried to deal with this problem could not provide significant recommendations due to the difficulty in study design. Therefore, we aim to study an animal model of spondylitis to approach this problem.

Methods. Proteoglycan-induced arthritis/spondylitis (PGIA/PGSp) is an established murine model that resembles peripheral arthritis as well as axial spondylitis leading to ankylosis of the affected joints. We aim to establish a system in PGIA/PGSp that combines imaging and

histopathology to evaluate and discriminate the two major hallmarks of AS: inflammation and new bone formation. Animal MRI will be performed to monitor spondylitis/arthritis of axial/peripheral joints over time in healthy (non-immunized) as well as untreated and treated (Etanercept) diseased (immunized) animals. To analyze the histopathological changes during the course of the disease MRI will be used to detect the typical manifestations (spondylitis/arthritis; progression to fatty bone marrow lesions; transition to ankylosis). Of interest are pro-inflammatory markers (IL-1, -6, TNF- α), markers of bone-remodelling (Dkk-1, RANKL, OPG, OSCAR), and adipocytokines (adiponectin, visfatin, leptin). To observe correlations of histopathological imprinting to serum markers is of great relevance in this respect. By starting treatment with Etanercept in one group of the animals as soon as the first signs of disease occur, we will be able to evaluate the effects of Etanercept on the course of the disease.

5. Abstracts without presentation

5.1

Long-term safety of Etanercept in patients with juvenile idiopathic arthritis (JIA)

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Background. Etanercept (Eta) has been the most frequently used biologic drug in patients with JIA. According to the national paediatric rheumatologic database, about one in four patients with polyarticular JIA received Eta in 2011. However, published data on its long-term safety are limited. The data of the JIA biologic registers BiKeR and JuMBO were used to determine the rates of serious adverse events or events of special interest in order to assess the long-term safety of Eta.

Methods. Patients who were included at start with Eta in the BiKeR registry and have been observed into adulthood were considered for this analysis. All adverse events recorded by physicians over the whole observation period (mean 6.7 years) were categorized on the basis of MedDRA. Total exposure-adjusted rates for serious adverse events (SAEs) and for events of special interest (i.e., deaths, malignancies, medically important infections [MII], and newly emerged other immune-mediated inflammatory diseases [IMID]) per 100 patient years (PY) were calculated.

Results. During the 1,965 years of Eta exposure in 431 patients (mean age: 20 years, mean disease duration: 11 years) 84 SAEs were recorded (4.3 SUEs/100 PY), of which less than 10% were possibly related to therapy. The SAE rates for each year of Eta exposure per 100 PY varied somewhat over the first nine years of treatment, but did not differ significantly. The JIA-associated mortality rate was 0.5% in this study population. Two deaths occurred in patients treated with Eta within the last three months before death, but no patient died in suspected causal relationship to Eta. Two malignancies were reported, resulting in 0.1 events per 100 PY of exposure. Twenty five MII were recorded which led to drug discontinuation in five patients. 75% of the MII occurred within the first three years of Eta treatment. The exposure-adjusted MII rate was 1.3 per 100 PY. Tuberculosis or other opportunistic infections were not registered. A total of 18 incidents IMID (0.9/100 PY) were reported: among them were eight cases with new onset inflammatory bowel disease and eight cases with uveitis.

Conclusions. The hitherto most comprehensive study of the long-term safety of Eta confirms the good tolerability of the substance. SAEs with possible relationship to therapy occur only rarely. However, reliable risk rates for events of particular interest can only be calculated in larger patient cohorts. Moreover, a comprehensive control group is necessary to put the results into perspective.

5.2

Analysis of S100 proteins S100A8, S100A9 und S100A12 in patients with psoriasis before, under and after treatment with Etanercept in order to evaluate the disease activity

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Background. Some data clearly showed an upregulation of the expression of S100 proteins A7 (Psoriasin), S100A8 (Calgranulin A), S100A9 (Calgranulin B) and S100A12 (Calgranulin C) in basal and suprabasal keratinocytes in psoriasis skin. Therefore, measurement of S100A7, S100A8/ S100A9 and S100A12 in serum during a treatment course in patients with psoriasis might be a less invasive method and an objective tool to evaluate the disease activity.

Methods. S100A7, S100A8/9, S100A12 were analysed in the sera of psoriasis patients treated with Etanercept over 24 weeks with a dose of 50 mg biweekly for 12 weeks and 50 mg once weekly the following 12 weeks. S100 levels were obtained on week 0 from n=26, on week 4 from n=26, on week 12 from n=21, on week 20 from n=15 and on week 24 from n=7 patients. Additionally S100A7 was analysed in sera of psoriasis patients (n=10) who underwent a therapy with narrowband ultraviolet (UV) B therapy at week 0, 4, 12 and 20 and from healthy donors (n=10) as control group. The serum levels were correlated with the PASI (Psoriasis Area Severity Index) of the patients on the mentioned time points.

Results. The data obtained show that S100A7 is significantly elevated in untreated psoriasis patients (mean 8.34 ng/ml, PASI >10/mean 3.92, PASI<10) in correlation to the disease activity measured by PASI compared to healthy donors (mean 1.22 ng/ml). Untreated psoriasis patients (n=25) with a PASI >10 have an increased serum level of S100A8/9 (mean 680.7 ng/ml) compared to patients treated 24 weeks with Etanercept and a PASI<10 (mean 305.5 ng/ml; p<0.01). A similar observation was made by investigations of S100A12 in sera of psoriasis patients with a PASI>10 (mean 150 ng/ml) before treatment compared to patients with PASI<10 (mean 92 ng/ml; p<0.05) after 24 weeks of Etanercept therapy. These changes have not been observed in the serum levels of S100A7 measured on week 0 compared to those measured on week 24, although a significant reduction of the PASI has been remarked. However the treatment course of S100A7 during Etanercept therapy, we saw a correlation to PASI with a reduction of PASI until week 12 followed by an upregulation of S100A7 over the next weeks, whereas the PASI increased not significantly.

Conclusions. These data show a significant correlation of S100A7, S100A8/ S100A9 and S100A12 measured in the sera of patients with psoriasis to the disease activity evaluated in PASI during a treatment course with Etanercept over 24 weeks.

5.3

TNF- α -induced activation of monocytes and its use for monitoring anti-TNF- α treatment

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Background. Activation of cells of the innate immune system plays an important role in the pathogenesis of juvenile idiopathic arthritis (JIA). Especially monocytes and macrophages exhibit pro- as well as anti-inflammatory properties, depending on their stage of activation. The important contribution of these cells is demonstrated by the fact that effective treatment regimens, such as anti-tumor necrosis factor α (TNF- α) agents, are specifically targeting phagocytes. The adjustment

of immunosuppressive therapy to the actual disease activity remains a difficult task for the physician. Therefore, this issue has to be especially considered in children, in whom the benefits and possible side effects of long-term immunosuppression must be carefully considered. Even though Etanercept treatment is very effective, 26% of patients initially do not respond to treatment. Common laboratory markers indicating activation of the immune system, e.g., the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level, reflect systemic rather than local activity in an inflammatory process. Studies published by our group have shown that S100A8 (myeloid-related protein 8, MRP8) and S100A9 (MRP14) are specifically secreted by activated human monocytes and directly promote inflammatory processes via induction of TNF- α and induce autoreactive T-cells in autoimmunity.

Methods. This project contains of a basic research part (A) in which the TNF- α induced activation of monocytes should be characterized and a translational part (B) that uses activation markers of phagocytes for monitoring anti-TNF- α treatment. A: Monocytes were activated by IL-1 or TNF- α and their gene expression profile analyzed by microarray technology (Affymetrix). B: Serum samples were collected from 74 patients before and after Etanercept treatment and clinical data was obtained. The serum samples obtained for the Dutch ABC registry will be used for S100 protein analyses as a surrogate marker for TNF- α -dependent inflammation.

Results. Both parts are still work in progress. A: We have analyzed the gene expression profile of IL-1 and TNF- α stimulated monocytes and defined differentially activated genes. The confirmation of these findings by independent methods is subject of the ongoing project. B: Paired samples have been collected in the last months and are analysed by S100 ELISA. Results are pending.

Conclusions. Since this is an ongoing study it is not eligible to draw conclusions. Nevertheless the first milestones (A) analyzing IL-1 and TNF- α gene expression and (B) recruiting patients to the study have been reached.

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Zusammensetzung: Enbrel 10 mg, -25 mg: 1 Durchstechfl. m. Plv. enth.: 10 mg bzw. 25 mg Etanercept. Sonst. Bestandt.: Pulver: Mannitol, Sacrose, Trometamol. 1 Fertigspritze m. Lsg.-mittel enth. Wasser f. Inj.-Zwecke. **Enbrel 25 mg/-50mg Inj.-Lsg. in Fertigspr. u. Enbrel 50 mg Inj.-Lsg. im Fertigpen (MYCLIC):** 1 Fertigspr. enth.: Etanercept 25 mg bzw. 50 mg, 1 Fertigpen enth. Etanercept 50 mg. Sonst. Bestandt.: Sacrose, Natriumchlorid, Argininhydrochlorid, Natriumdihydrogenphosphat-Dihydrat, Natriummonohydrogenphosphat-Dihydrat, Wasser f. Inj.-Zwecke. Etanercept wird gentechn. aus der Eierstockzelllinie d. Chinesischen Hamsters hergestellt. **Anwendungsgebiete:** **Enbrel 25 mg u. 50 mg:** *Rheumatoide Arthritis:* Enbrel ist in Komb. m. Methotrexat (MTX) zur Behandl. d. mittelschweren bis schweren aktiven rheumatoiden Arthritis (RA) bei Erw. indiziert, wenn Ansprechen auf Basistherapeutika (einschl. MTX - sofern nicht kontraind.) unzureichend ist. Enbrel kann im Falle einer Unverträglichk. gegenüber MTX od. wenn eine Forts. d. Behandl. m. MTX nicht mögl. ist, als Monother. angewendet werden. Behandl. der schweren, aktiven u. progressiven rheumatoiden Arthritis bei Erw., die zuvor nicht m. MTX behandelt worden sind. Enbrel reduziert als Monother. od. in Komb. m. MTX d. Fortschreiten d. radiolog. nachweisbaren strukturellen Gelenkschädig. u. verbessert d. körperl. Funktionsfähigk. *Psoriasis-Arthritis (Arthritis psoriatica):* Behandl. d. aktiven u. progressiven Psoriasis-Arthritis bei Erw., wenn Ansprechen auf vorhergehende Basisther. unzureichend ist. Enbrel verbessert d. körperl. Funktionsfähigk. bei Pat. m. Psoriasis-Arthritis u. reduziert d. Fortschreiten d. radiolog. nachweisbaren strukturellen Schädig. peripherer Gelenke b. Pat. m. polyartikulären symmetrischen Subtypen d. Erkrank. *Morbus Bechterew (Spondylitis ankylosans):* Behandl. d. schweren aktiven Morbus Bechterew bei Erw., die unzureichend auf konventionelle Behandl. angesprochen haben. *Plaques-Psoriasis:* Behandl. Erwachsener m. mittelschwerer bis schwerer Plaque-Psoriasis, die auf eine andere syst. Ther. wie Ciclosporin, MTX od. Psoralen u. UVA-Licht (PUVA) nicht angesprochen haben od. bei denen eine Kontraind. od. Unverträglichk. einer solchen Ther. vorliegt. **Enbrel 10 mg sowie zusätzl. f. Enbrel 25 mg u. 50 mg:** *Juvenile idiopathische Arthritis (JIA):* Behandl. d. Polyarthritis (Rheumafaktor-positiv od. -negativ) u. d. erweiterten (extended) Oligoarthritis bei Kindern u. Jugendl. ab 2 J., die unzureichend auf MTX-Behandl. angesprochen haben od. MTX-Behandl. nicht vertragen. Behandl. d. Psoriasis-Arthritis (Arthritis psoriatica) bei Jugendl. ab 12 J., die unzureichend auf MTX-Behandl. angesprochen haben od. MTX-Behandl. nicht vertragen. Behandl. d. Enthesitis-assoziierten Arthritis bei Jugendl. ab 12 J., die unzureichend auf eine konventionelle Ther. angesprochen haben od. eine konventionelle Ther. nicht vertragen. *Plaques-Psoriasis bei Kindern u. Jugendl.:* Behandl. d. chron. schweren Plaque-Psoriasis bei Kindern u. Jugendl. ab 6 J., die unzureichend auf eine and. system. Ther. od. Lichtther. angesprochen haben od. sie nicht vertragen. **Gegenanzeigen:** Überempfindlichk. gegen den Wirkstoff od. einen d. sonst. Bestandteile. Nicht anw. bei Sepsis od. Risiko einer Sepsis (cave: mögl. Erhöhung d. Mortalität bei bestehender Sepsis). Ther.-Beginn nicht bei aktiven Infekt., einschl. chron. od. lokalisierter Infekt. od. bei Pat. m. aktiver Tuberkulose. Pat. m. inaktiver Tuberkulose nur nach entspr. Anti-Tuberkulose-Ther. u. sehr sorgf. Nutzen/Risiko-Abwägung. HBV-Überträger u. Pat. m. bes. HBV-Infekt.-Risiko überprüfen, ggf. Enbrel-Anw. erst nach Anti-HBV-Ther.; **Warnhinweise und Vorsichtsmaßnahmen:** Pat. vor, währ. u. nach Enbrel-Behandl. auf Infekt. hin untersuchen. Vorsicht walten lassen bei Pat. m. wiederkehrenden od. chron. Infekt. i. d. Vorgeschichte od. m. Begleiterkrank., die Infekt. begünstigen können (z. B. fortgeschrittener oder schlecht eingestellter Diabetes), sowie bei neuentwickelten Infekt. Unter Anw. v. Enbrel wurden schwerw. Infekt., Sepsis, Tuberkulose (Tb) u. opportunistische Infekt., einschl. invasiver Pilzinfekt., Listeriose u. Legionellose beobachtet (in einigen Fällen m. Todesfolge durch Nichterkennung u. verzögerte Behandl.). Pat.-Risiko für relevante opportunist. Infekt. berücksichtigen. Ther.-abbruch bei Entwickl. v. schwerer Infekt., sowie bei Auftreten schwerw. allerg. od. anaphylakt. Reakt. Vor Behandlungsbeginn alle Pat. auf aktive u. inaktive (latente) Tb hin untersuchen. Pat. anweisen, bei Tb-Sympt. ärztl. Rat einzuholen. Reaktivierung d. Hepatitis-B-Virus (HBV) wurde v. Pat. berichtet, die chron. Träger dieses Virus sind u. TNF-Antagonisten, einschl. Enbrel, erhalten haben. Besondere Vors. bei Pat. m. Blutdyskrasie in d. Anamnese, bei Auftreten v. Sympt. eindringl. Abklärung; bei nachweisl. Blutdyskrasie Enbrel absetzen. Bei starker Exposition gegenüber Varizella-Viren Behandl. vorübergehend abbrechen, ggf. Prophylaxe m. Varizella-zoster-Immunglobulinen. Regelm. Hautuntersuch. empf., da unter Behandl. m. TNF-Antagonisten, einschl. Enbrel, über Melanome und nicht-melanozytären Hautkrebs (NMSC) berichtet wurde. Besondere Vors. bei Pat. m. Herzinsuffizienz; Pat. m. Hepatitis C i.d. Anamnese wg. mögl. Verschlecht.; Enbrel nicht zur Behandl. v. Alkohol-Hepatitis anw.; Vorsicht b. Pat., die auch an mittelschw. bis schwerer Alkohol-Hepatitis leiden. Komb. Anw. v. Enbrel m. Anakinra oder Abatacept sowie Anw.

v. Enbrel bei Wegener'schen Granulomatose wird nicht empf.; bei gleichz. medikamentöser Diabetes-Behandl. Fälle v. Hypoglykämie (ggf. Dosisred. v. Antidiabetika notw.); Vorsicht b. älteren Pat., insb. auf mögl. Infekt. achten. Keine gesicherten Erkenntnisse über Langzeitsicherheit v. Enbrel bei gleichzeitiger Gabe m. anderen antirheumatischen Basistherapeutika (DMARD). Anw. in Schwangerschaft u. Stillzeit nicht empf. Mögl. Risiko f. die Entwickl. v. Lymphomen, Leukämie od. and. hämatopoetischen malignen Erkrank. od. soliden Tumoren kann derzeit bei Ther. m. TNF-Antagonisten nicht ausgeschlossen werden; deshalb Behandl. abwägen bei Pat. m. maligner Erkrankung i.d. Anamnese od. Entwickl. v. maligner Erkrank.; Sicherheit u. Wirksamk. v. Enbrel bei Pat. m. Immunsuppression od. chron. Infekt. wurden bisher nicht untersucht. Lebendimpfstoffe sollten nicht gleichzeitig verabreicht werden. Sorgf. Nutzen-Risiko-Analyse, einschl. neurolog. Untersuchung, bei bestehender od. jüngst neu aufgetretener Entmarkungskrankheit od. evtl. erhöhtem Risiko f. Entwickl. einer Entmarkungskrankheit. Anw. v. Enbrel in Komb. m. anderen syst. Ther. od. Lichtther. zur Behandl. v. Psoriasis wurde nicht untersucht. *Nur für Enbrel 25 mg / 50 mg Fertigspritze u. Enbrel 50 mg Fertigpen:* Kanülenkappe d. Fertigspritze bzw. d. Fertigpens enth. Latex (Trockenkautschuk), das Überempfindlichkeitsreakt. verursachen kann. **Nebenwirkungen:** Basierend auf Beobachtungen aus klin. Studien bei Erw. u. Berichten n. Markteinf.: **Sehr häufig:** Reakt. an d. Inj.-stelle, ggf. passagere „Recall“-Reakt. an d. Inj.-stelle, Infekt. (einschl. Infekt. d. oberen Atemwege, Bronchitis, Zystitis, Hautinfekt.). **Häufig:** Allerg. Reakt., Fieber, Bildung v. Autoantikörpern, Pruritus. **Gelegentl.:** Schwere Infekt. (einschl. Pneumonie, Erysipel, sept. Arthritis, Sepsis, parasitäre Infekt.), nicht-melanozytärer Hautkrebs, Thrombozytopenie, systemische Vaskulitis, Uveitis, Skleritis, interstitielle Lungenerkrankung (einschl. pulmonale Fibrose u. Pneumonitis, z.T. letal), Angioödem, Urtikaria, Hautausschlag, psoriasisartiger Hautausschlag, Psoriasis (einschl. Erstmanifestationen od. Verschlecht. u. pustulöse Formen, primär Handflächen u. Fußsohlen). **Selten:** Tuberkulose (inkl. Miliartuberkulose u. extrapulmonärer Tuberkulose), opportunist. Infekt. (einschl. invasive Pilz-, Protozoen-, Bakterien-, u. atypische Mycobakterien-Infekt. u. Legionellose), Lymphom, Melanom, Anämie, Leukozytopenie, Neutropenie, Panzytopenie, schwere allerg./anaphylakt. Reakt. (einschl. Angioödem, Bronchospasmus), Sarkoidose, Anfälle, ZNS-entmyelinisierende Ereign. m. Verdacht auf multiple Sklerose od. lokalisierte entmyelinisierende Zustände wie Neuritis nervi optici u. Querschnittsmyelitis; Verschlecht. v. Herzinsuff., erhöhte Leberenzyme, autoimmune Hepatitis, kutane Vaskulitis (einschl. leukozytoklastische Vaskulitis), Stevens-Johnson-Syndrom, Erythema multiforme, subakuter, kutaner od. diskoider Lupus erythematoses, Lupus-ähn. Syndrom, entmyelinisierende Erkrank. d. ZNS. **Sehr selten:** Aplastische Anämie, toxische epidermale Nekrolyse, periphere demyelinisierende Ereignisse (einschl. Guillain-Barré-Syndr., chron.-entzündl. demyelinisierende Polyneuropathie, demyelinisierende Polyneuropathie u. multifokale motorische Neuropathie). **Häufigkeit nicht bekannt:** Listeriose, Hepatitis B-Virus-Reaktivierung, Leukämie, Merkelzell-Karzinom, Makrophagen-Aktivierungs-Syndrom. *In Studien zur RA m. (Dauer bis zu 48 Mon.) wurden schwerw. Infekt. beobachtet einschl.:* Abszess, Bakteriämie, Bronchitis, Bursitis, Erysipel, Cholezystitis, Diarrhoe, Divertikulitis, Endokarditis (vermutet), Gastroenteritis, Hepatitis B (Reaktivierung b. chron. HBV-Trägern), Herpes zoster, Unterschenkelgeschwür, Mundinfekt., Osteomyelitis, Otitis, Peritonitis, Pneumonie, Pyelonephritis, Sepsis, septische Arthritis, Sinusitis, Hautinfekt., Hautgeschwür, Harnwegsinfekt., Vaskulitis, Wundinfekt.; Nach Markteinf. wurde über versch. Malignome (einschl. Brust- u. Lungenkarzinom sowie Lymphom) berichtet. *Bei Komb. v. Enbrel m. MTX (Studie):* Raten d. schwerw. Infekt. waren gegenüber d. Monother. ähnl., jedoch ist ein Anstieg d. Infektionsrate bei Kombi-Therapie mögl. *In Studien zur Plaque-Psoriasis:* Schwere Infekt. wie Erysipel, Gastroenteritis, Pneumonie, Cholezystitis, Osteomyelitis, Gastritis, Appendizitis, Streptokokken-Fasziitis, Myositis, sept. Schock, Divertikulitis, Abszess. *Bei gleichz. Anw. v. Enbrel u. Anakinra* wurde bei erw. Pat. ein erhöhtes Risiko f. schwerw. Infekt. u. Neutropenie beobachtet. *Nebenwirk. bei Kdrn. u. Jugendl.:* Diese waren i. A. denen d. Erw. ähnl. *Nebenwirk. bei Kdrn. u. Jugendl. m. JIA:* Häufiger als bei Erw. waren: Kopfschmerzen, Übelkeit, Erbrechen u. Unterleibsschmerzen. Es gab Berichte über chron.-entzündl. Darmerkrank.; Schwerw. NW umfassten: Varizellen-Infektion m. Zeichen u. Sympt. v. aseptischer Meningitis (ohne Folgeschäden), Blinddarmentz., Gastroenteritis, Depression/Persönlichkeitsstör., Hautgeschwür, Ösophagitis, Gastritis, sept. Schock, Typ I Diabetes mellitus, Weichteilinfekt. u. postoperative Wundinfekt. Weitere Informationen siehe Fach- u. Gebrauchsinformation. **Abgabestatus:** Verschreibungspflichtig. **Inhaber der Zulassung:** Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9 NJ, Vereinigtes Königreich. **Repräsentant in Deutschland:** PFIZER PHARMA GmbH, 10785 Berlin. Stand: Dezember 2012