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Tight Junctions

7. Interdisziplinäres rheumatologisches/ dermatologisches Forschungssymposium

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Abstracts

Guest Editors Supplement

Prof. Dr. med. Ulf Müller-Ladner, Bad Nauheim
Prof. Dr. med. Thomas Schwarz, Kiel

1. Prognosis and outcome

1.1

Clinically important worsening (CIW) of rheumatoid arthritis disease activity requiring an increase in therapy can be identified using a combined patient and physician report of flare

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Background. A reference point for clinically important worsening (CIW) of rheumatoid arthritis (RA) disease activity requiring retreatment or escalation is needed for randomized trials of treatment withdrawal. These studies are usually performed in patients (Pt) in states of low disease activity (LDA) or remission (REM). Restarting RA therapy needs a Pt-MD concordant assessment of worsening ("flare") to maximize adherence. Here, we examine the construct and convergent validity of a combined Pt-MD concordant report of flare that indicates CIW in patients who are in LDA/REM.

Methods. CATCH (Canadian early Arthritis CoHort) Pts were eligible for the study if they were in DAS28 REM or LDA at the first (V1) of two sequential visits (3 or 6 months apart). RA flare was assessed at the second visit (V2). Patients reported if their RA was flaring (yes/no), and, if yes, the severity and duration. Concurrently, MDs classified them as flaring (yes/no). Changes in disease activity and treatment, OMERACT core flare domains, MD measures, inflammatory markers, and DAS28 were assessed in Pts reporting flare, MDs classifying flare, and when Pts and MDs were concordant in identifying flare.

Results. Of the 849 RA patients who completed the OMERACT flare questions twice between November 2011 and October 2014, 360 (42%) were in LDA or REM at the first of the paired visits. Patients most often reported a flare duration lasting > 14 days in Pt-MD-concordant flares, with a mean (MD report) severity rating of 5.0 (2.3). DAS28 worsening was less in MD reports of flare, DAS28 0.9 (1.3) vs 1.8 (1.2) in Pt-MD-concordant flare. Prior treatment reduction/withdrawal was observed in 36% of Pt-MD-concordant flares with subsequent treatment addition in 61% at/after the second "flare." Mean differences in the measures of RA disease activity (PROs, clinical, and laboratory assessments), were significant in Pt-reported flare, and of greater magnitude with concordant Pt-MD flare. This was notable for all measures in the existing RA core set for monitoring disease activity and the expanded OMERACT flare core set.

Conclusion. A concordant Pt-MD report of flare may provide a feasible assessment of CIW of RA disease activity associated with a worsening in ACR RA core set measures and domains in the expanded OMERACT flare core set. This anchor for CIW is often associated with stopping or reducing treatment and with subsequent increases in therapy. These data provide a rationale for using this Pt-MD anchoring construct to identify CIW for existing and new RA disease activity measures.

1.2

Diagnosis of subclinical arthritis: comparing clinical examination, joint ultrasound, magnetic resonance imaging, and biomarkers

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Background. The need for anti-inflammatory or immunosuppressive treatment of juvenile idiopathic arthritis (JIA) is currently driven by the presence or absence of active arthritis. Joint inflammation, however, exists on a spectrum from clinically overt inflammation to subclinical inflammation, i. e., inflammation that is not clinically detectable. Often, the presence of joint damage, e. g., contractures, makes the diagnosis of active arthritis difficult. Subclinical arthritis may, for example, be potentially detected via ultrasound, magnetic resonance imaging (MRI) or biomarker analy-

sis. Previous studies have shown that the presence of elevated biomarkers during clinically inactive disease during treatment indicates a higher risk of flare upon discontinuation of treatment. However, whether or not subclinical inflammation is generally meaningful remains unclear. Furthermore subclinical arthritis has not been clearly defined. Therefore, the goal of the study is to determine and correlate measures of subclinical arthritis in children with JIA.

Methods. We designed a study planning to enroll patients diagnosed with JIA who have clinically inactive disease, but in whom inactive disease is questionable or hard to assess, e. g., because of the presence of joint damage or contractures. Patients undergo clinical joint examination by a certified joint assessor, a standardized joint ultrasound of 18 relevant joints by two independent assessors, a whole-body MRI with contrast agent and biomarker analysis, i. e., high-sensitivity CRP and S100A12 testing. These data are compared and correlated to determine patterns of subclinical arthritis.

Results. Subject enrollment will begin shortly and results are not currently available.

Conclusion. The concept of arthritis ranging from subclinical inflammation to overt clinical inflammation remains to be tested and reliable measures of subclinical inflammation have to be identified. This may prove valuable in steering anti-inflammatory treatment in JIA.

1.3

Prevalence of anti-drug antibodies (ADA) and anti-nuclear antibodies (ANA) and their relevance for the therapeutic response in patients with psoriasis

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Background. Psoriasis is a chronic inflammatory, Th17-mediated autoimmune disease of the skin and joints affecting 0.5–1% of children and 2–3% of the adult population. Approximately 20–30% of patients with psoriasis of the skin also suffer from psoriatic arthritis. Patients with psoriasis often report an impaired quality of life. In addition comorbidities are frequently found. Modern therapies with small molecules or antibodies targeting TNF or p40 improve psoriasis and psoriatic arthritis. However, clinical practice shows that there is a substantial number of patients with primary or secondary loss of response to the aforementioned therapeutics. The occurrence of anti-drug antibodies (ADA) could be an explanation for the loss of response in patients treated with biologics. However, other mechanisms may also exist. Interestingly, the development of anti-nuclear antibodies (ANA) has also been reported in patients treated with TNF antagonists.

Methods. The goal of our study is to determine the prevalence of ADA and ANA in secondary non-responders. In detail we want to analyze whether certain therapies promote the general development of autoantibodies or allergen-specific antibodies, or whether they only tend to induce ADA. We plan to include 200 patients by the end of the study.

Results. Here, we present some preliminary data.

2. From nano to macro

2.1

Biological therapies and intestinal microbiota: a longitudinal study in diverse disease phenotypes

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Background. Immune-modulating recombinant antibodies (such as anti-TNF antibodies) are the most effective therapies for a broad and heterogeneous group of disease, including rheumatoid arthritis and inflammatory bowel disease. The pathogenesis of these diseases is argued around the microbial-driven activation of the immune cascade and a cytokine imbalance; however, the impact of such targeted cytokine blockade on intestinal microbial communities is poorly understood. This study is aimed at determining the impact of biological therapies on microbiota in a cohort of patients with intestinal and non-intestinal diseases.

Methods. We enrolled patients with rheumatoid arthritis and inflammatory bowel disease in this longitudinal study. Healthy volunteers with no known disease served as the control group. Fecal samples were collected at the start of therapies and on day 1, day 3, after 1 week, 1 month, and 6 months of therapeutic interventions. DNA was extracted from fecal samples and the V4 region of the 16S rRNA gene was sequenced using the MiSeq Illumina platform.

Results. We observed significant differences in the proportion of major bacterial groups (Firmicutes and Actinobacteria) after biological therapies. Likewise, microbial composition and structure (beta diversity) were significantly altered after therapy compared with the changes in the healthy volunteers within the same time frame. We are now linking these therapy-associated microbial changes to the predicated microbial metabolic profiles; results will be presented at the conference.

Conclusion. Our data suggest a marked influence of biological therapies on microbial composition and structure.

2.2

High-resolution MRI in psoriatic arthritis: first results of the ADAM (Analysis of the Dactylitic Mélange) study

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Background. Psoriatic arthritis (PsA) affects up to one third of patients with psoriasis. Dactylitis ("sausage" shaped digit) and distal interphalangeal (DIP) joint arthritis occur in up to 50%, ranging from painful to often asymptomatic swollen digits. Conventional radiography is still the standard imaging method used to detect bony alterations in PsA, while new imaging techniques such as ultrasound and magnetic resonance imaging (MRI) are going to play an increasing role in the sensitive visualization of soft tissue inflammation (e.g., synovitis, enthesitis) and specific bony changes (bone marrow edema and erosions) using multiplanar views. In addition, small joint MRI coils offer the opportunity to generate high-resolution images and new insights into the pathogenesis of affected PsA finger joints

Methods. Based on the advantages of these new imaging modalities we initiated the ADAM study in July 2015 to evaluate the value of high-resolution MRI (3-T) in PsA finger arthritis before and after etanercept as a tool for defining morphological aspects of dactylitis that might give hints for therapy response or non-response.

Results. First results show typical formations of enthesitis and dactylitis in the highest resolution. By generating follow-up MRI data (after 6 months), we hope to differentiate responders from non-responders, respectively to be able to image an individual prognostic MRI profile and pattern, allowing the risk for remission or progression to be defined.

3. Clinical studies

3.1

Efficacy of etanercept on radiographic progression in adult patients with rheumatoid arthritis or psoriatic arthritis: results from the second interim analysis of a German non-interventional, prospective, multi-center study

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Background. It is known from the COMET trial that patients with early rheumatoid arthritis (RA) have a better chance of reaching clinical remission and radiographic non-progression if etanercept (ETN) treatment is started early. However, the proportion of patients with RA or psoriatic arthritis (PsA) achieving remission and radiographic non-progression in routine rheumatological care is not known.

Methods. 1,600 adult RA and 400 PsA patients will be included in the study. Plain radiographs of hands and feet are taken at baseline (< 3 months prior to or after the start of ETN treatment) and after 12 to 18 and after 36 months' follow-up. The primary outcome measure is the change in radiographic progression using the "van der Heijde modified Sharp score" (mTSS) for RA patients and the "van der Heijde modified Sharp score adapted" (mTSS adapted) for PsA patients by two blinded readers. Further outcome parameters such as disease activity score (DAS28) and (serious) adverse events are recorded regularly.

Results. 282 RA (77% females) and 87 PsA patients (51% females) were evaluated for this interim analysis. The median disease duration at baseline was 5.3 (range: 0–46) years (RA) and 4.3 (0–37) years (PsA). At baseline, mean mTSS in RA patients was 22.1 ± 33.2 (n = 136), mean mTSS adapted in PsA patients was 21.6 ± 30.6 (n = 34). Radiographs after 52–78 weeks were available for 131 RA (32 PsA) patients with a mean annualized radiographic progression of 1.4 ± 6.4 (–0.871 ± 4.2) under ETN therapy. During ETN treatment, 29.8% RA (28.1% PsA) patients experienced no change (–0.5 to 0.5) and 30.5% RA (43.8% PsA) an improvement (< –0.5). In total, slightly more PsA than RA patients were considered to have no radiographic progression (60.3% RA vs 71.9% PsA, change in mTSS (adapted) ≤ 0.5 from baseline). Sixty-five RA (16 PsA) patients had a historic (i.e., 12–48 months prior to baseline) and a baseline X-ray, with a mean annualized radiographic progression of 3.7 ± 21.3 (2.1 ± 3.5). Comparison between the annualized radiographic progression under ETN treatment and previous disease progression (before baseline X-ray) revealed lower annual radiographic progression under therapy with ETN in both treated groups (Δ annual progression under ETN minus annual progression before baseline; RA: n = 61, –3.6 ± 22.1, p = 0.205; PsA: n = 14, –3.5 ± 6.1, p = 0.049). In RA (PsA) patients, the DAS28 decreased from a mean baseline value of 4.6 ± 1.3 (4.2 ± 1.0) to 2.9 ± 1.2 (2.4 ± 1.0) at week 78, indicating an important decrease in disease activity under ETN treatment. At week 78, fewer RA than PsA patients reached remission (DAS28 < 2.6; 44.6% RA vs 60.7% PsA). Treatment with ETN was well tolerated and no new safety signals were observed.

Conclusion. The results of this interim analysis suggest that treatment with ETN slows radiographic progression and reduces disease activity in RA and PsA patients in routine clinical care.

4. Answers to clinical questions

4.1

The dynamics of IgG1 and IgG4 ACPA levels during therapy in rheumatoid arthritis

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Background. Citrullinated vimentin (MCV) and cyclic citrullinated peptides (CCP) have been identified as autoantigens in RA and anti-MCV and anti-CCP antibodies turned out to be highly specific for RA and of prognostic value. Our long-term goal is to elucidate the specific involvement of these autoantibodies against citrullinated peptide antigens (ACPA) in the pathogenetic processes leading to RA.

We have previously shown that IgG1 and IgG4 are the predominant subclasses among antibodies against CCP and MCV in RA and the levels of IgG4 are independent of the duration of the disease. This predominance of the IgG4 subclass in autoantibodies does not reflect a general skewing towards IgG4 as the overall serum titers and antibodies directed against Varicella zoster virus show a normal distribution with IgG1 > IgG2 > IgG3 > IgG4. Cross-sectional studies from our laboratory suggested that predominantly IgG4-aCCP and IgG4-aMCV titers are upregulated in patients receiving biologicals compared with those on DMARD therapy, and that these titers also correlate with the DAS28.

Methods. Our investigator-initiated research project is aimed at elucidating whether these different IgG4 autoantibody titers reflect either different disease entities or a response to treatment. To that extent we here perform a longitudinal study and include patients at a change of therapy who are started on either MTX or a (different) biological. We draw blood at the initial time point and at 3, 6, and 9 months thereafter, and we compare autoantibody titers to the various blood cell populations, to serum cytokines, to bone resorption markers, and various clinical parameters.

Results. Preliminary results confirm that a change in the DAS28 correlates with a change in IgG4-aCCP titers; however, the latter is independent of the systemic inflammatory marker CRP. Moreover, it appears that the initial IgG4-aCCP titer is predictive of therapy response. Finally, neither MTX nor biological therapy leads to a reduction of bone resorption markers within the first 3 months.

Conclusion. Completion of our longitudinal study will clarify the involvement of IgG4-ACPA in the pathogenesis of RA and the patients' response to therapy.

4.2

Analyzing the longitudinal efficacy of a combined treatment with TNF- α inhibitors plus functional therapy in polyarticular JIA reveals benefit in functional capacity

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Background. Currently, 33 % of JIA patients with polyarticular course are treated with biologics (1). Substantial improvements according disease activity may be achieved using TNF- α inhibitors (2). Nevertheless, many JIA patients still suffer from joint impairments that have an influence on everyday functions and activity levels. The aim of this work was to verify the effects of a combined treatment including TNF- α inhibitors and functional treatment on the functional capacity of polyarticular JIA patients.

Methods. A prospective longitudinal study was initiated in polyarticular JIA patients, in whom treatment with TNF- α inhibitors who were intended to be treated because of high disease activity. Patients started a combination therapy with TNF- α inhibitors plus functional therapy and have been monitored on everyday functions capacity. The measurements

included: balance control (S3 check, TST, Großhoefflein), daily activity assessment (Step Watch, Orthocare Innovations, USA), clinical assessment, and 3D gait analysis using the PiG-GAP model (3) (Vicon, London). The gait was evaluated using the Gait Deviation Index (4) to consider joint-specific impairments. The first measurement (T0) was performed before introducing TNF- α inhibitor therapy with included 37 JIA patients. Despite 12 dropouts, the longitudinal data of 25 patients could be collected after 9.8 months (12 female/13 male; T0: 13.4 $\pm$ 3.4 years, 157 $\pm$ 20 cm, 50.0 $\pm$ 21.3 kg, active joints: 7.6 $\pm$ 11.0, JADAS-71: 18.2 $\pm$ 14.2, disease duration: 6.1 $\pm$ 5.6 years; T1: 14.2 $\pm$ 3.4 years, 160 $\pm$ 19 cm, 53.5 $\pm$ 22.2 kg, active joints: 1.1 $\pm$ 1.6, JADAS-71: 6.0 $\pm$ 7.1). Statistical comparisons were carried out using paired and unpaired t tests ($p < 0.05$).

Results. In the clinical parameters, summarized using the JADAS-71, JIA patients ($n = 25$) significantly improved during therapy ($p = 0.001$). At T0, 18 JIA patients showed clinically abnormal gait patterns. After the therapy period we found an overall statistically significant improvement ($p = 0.002$), but 11 patients still had smaller gait deviations. In sensory motor control (T0: $p = 0.022$; T1: $p = 0.004$) in addition to stability capacity (T0 and T1: $p < 0.001$), JIA patients showed better results than the healthy reference group [5]. Functional abilities in balance remained constant between T0 and T1. The mean daily activity level was measured in $n = 10$ JIA patients and showed no changes in total activity minutes ($p = 0.721$), but a significant increase in steps/minute ($p = 0.028$).

Conclusions. This is one of the first studies to analyze the effects of TNF- α inhibitors on the functional deficits during everyday activities in polyarticular JIA patients. While the majority of patients were demonstrated to have benefits, especially in gait function and daily activity, another 44 % still show functional limitations at T1. We propose that these effects would be much more pronounced in a population of polyarticular JIA patients with a shorter course of disease before initiation of the TNF- α inhibitor treatment. An unexpected result concerned the positive balance performance of JIA patients. This may result from earlier physiotherapy due to the long disease duration and/or permanent posture adaptations based on pain-relieving postures.

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4.3

The impact of MTX and etanercept on periodontitis in patients with rheumatoid arthritis: a 48-week observational study

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Background. Rheumatoid arthritis (RA) and periodontal disease (PD) are two of the most common chronic inflammatory diseases. There are epidemiological and immune pathogenic similarities between the two diseases. Previous data indicate a higher treatment response in patients with RA when existing PD is treated. The influence of DMARDS or TNF inhibitors on PD is still controversial. Study aims: 1. How are clinical signs of PD influenced by treatment with Anti-TNF- α ? 2. How does bacterial growth in gingival fluid change under Anti-TNF- α therapy?

Methods. Eight patients with RA and proven PD who were receiving MTX therapy, and 13 patients with RA and proven PD who were receiving etanercept 50 mg weekly in addition to an existing MTX therapy were includ-

ed. All patients had positive rheumatoid factors and ACPA. A dental examination was carried out before the beginning of each therapy and after 24 and 48 weeks. All teeth were examined at six points per tooth for plaque deposits, the occurrence of bleeding on probe contact (BOP), and attachment loss (AL). Smears for molecular genetic determination of the bacterial count of 11 PD-pathogenic bacterial strains were performed in weeks 0, 24, and 48. None of the patients received a specific treatment for PD. Rheumatological examinations including DAS 28, SDAI, ESR, CRP, FFbH, and HAQ were performed in weeks 0, 16, 24, 32, and 48.

Results. Eight out of eight MTX patients and 11 out of 13 MTX + etanercept patients completed the study. In both groups, significant reductions in DAS 28, morning stiffness, and inflammation parameters were proven. The median MTX dose in both groups was 15 mg weekly, the median prednisolone dose was 7.5 mg daily. No significant change in the course of the disease resulted in the number of bacteria in the pockets of the tooth, the plaque deposits, and the loss of attachment in both groups. The bleeding on contact showed an increase of 19.2% in the MTX group and by 14.7% in the MTX + etanercept group ($p = 0.0057$).

Conclusion. The increased occurrence of bleeding on contact in both groups can be interpreted as an expression of gingival inflammation. No significant difference between the MTX and the MTX + etanercept groups could be found. An expected increase in bacterial count in the tooth pockets under immunosuppression could not be proven. Regular dental examinations, as well as dental hygiene measures in patients with RA are independently advised during therapy.

A

Aden K	2.1
Alten R	1.1

B

Beck L	1.2
Bethge J	2.1
Bingham CO	1.1
Brandt B	2.1
Bücheler M	3.1

C

Choy EH	1.1
Claas H	1.2

E

Engelmann R	4.1
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F

Föll D	1.2
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G

Ghoreschi K	1.3
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H

Haas J-P	4.2
Hartmann M	4.2
Hieke M	4.3
Holzinger D	1.2
Hrdlicka P	4.3

K

Klopsch T	3.1
Kneitz C	4.1
Kouba M	4.3

L

Lippe R	3.1
Löschmann P-A	3.1

M

Merker J	4.2
Müller-Hilke B	4.1

N

Nikolaus S	2.1
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O

Ostendorf B	2.2
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R

Rau R	3.1
Rehman A	2.1
Rosenbaum D	4.2
Rosenstiel P	2.1
Rudolph S-E	4.3

S

Schiborr M	1.2
Schreiber S	2.1
Schröder JO	2.1
Schwartz A	4.2
Sewerin P	2.2

V

Volc S	1.3
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W

Wassenberg S	3.1
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Z

Zeuner R	2.1
Zuber M	4.3

Lantarel® 2,5 mg/7,5 mg/10 mg; Tabletten **Lantarel® FS 7,5 mg/10 mg/15 mg/20 mg/25 mg;** Fertigspritze; Injektionslösung i.m./i.v.s.c.
Wirkstoff: Methotrexat-Dinatrium **Zusammensetzung:** Wirkstoff: Tbl.: 1 Tbl. enth. 2,74 mg/8,22 mg/10,96 mg Methotrexat-Dinatrium (entspr. 2,5 mg/7,5 mg/10 mg Methotrexat). Inj.-Lsg.: 1 Fertigspritze mit 0,3 ml/0,4 ml/0,6 ml/0,8 ml/1 ml Inj.-Lsg. enth. 8,22 mg/10,96 mg/16,44 mg/21,92 mg/27,41 mg Methotrexat-Dinatrium (entspr. 7,5 mg/10 mg/15 mg/20 mg/25 mg Methotrexat). **Sonstige Bestandteile:** Tbl.: Lactose, Maisquellstärke, Magnesiumstearat. Inj.-Lsg.: Natriumchlorid, Natriumhydroxid (zur pH-Wert-Einstellung), Wasser f. Inj.-zwecke. **Anwendungsgebiete:** Schwere Formen der aktiven rheumatoiden Arthritis (chron. Polyarthritiden), wenn Ther. mit anderen Basistherapeutika od. NSAIDs nicht ausreichend wirksam ist od. nicht vertragen wird, od. bei primär besonders aggressiv verlaufenden („malignen“) Formen der rheumatoiden Arthritis (chron. Polyarthritiden). Polyarthritische Formen der schweren aktiven juvenilen idiopathischen Arthritis (JIA) ab dem 3. Lebensj. bei mangelndem Ansprechen auf NSAIDs. Schwere Formen der Psoriasis vulgaris, insb. vom Plaque-Typ, u. der Psoriasis arthropathica, die mit einer konventionellen Ther. nicht ausreichend behandelbar sind. **Gegenanzeigen:** Bekannte Überempfindlichk. gegen MTX od. einen der sonst. Bestandteile, Nierenfunktionsstör. (Kreatinin-Clearance < 60 ml/min), Leberschäden (alkoholbedingte od. and. chron. Lebererkrank.), vorbestehende Erkrank. des blutbild. Systems, erhöhter Alkoholkonsum, Immundefizienz, schwere od. bestehende Infektionen, Ulzera des Magen-Darm-Traktes, Schwangerschaft, Stillzeit. **Vorsicht:** bei eingeschränkter Nierenfunkt.; Zuständen, die zur Dehydratation führen; patholog. Flüssigkeitsansammlungen in Körperhöhlen, Insulinpflichtigen Diabetes mell.; Einschränkung d. Lungenfunkt., Vorliegen v. inaktiven, chron. Infekt. hinsichtl. mögl. Aktivierung, gleichz. UV-Bestrahlung, älteren Pat. **Nebenwirkungen:** *Sehr häufig:* Appetitlosigkeit, Übelkeit, Erbrechen, Bauchschm., Entzünd. u. Ulzerationen d. Mund- u. Rachenschleimhaut; Anstieg d. Leberenzyme (ALAT [GPT], ASAT [GOT], alkal. Phosphatase u. Bilirubin). *Häufig:* Leukozytopenie, Thrombozytopenie, Anämie, Diarrhoe, Lungenkomplikation auf Grundlage einer interstit. Alveolitis/Pneumonitis (auch Todesfälle), m. Sympt. wie allg. Krankheitsgefühl, trockener Reizhusten, Kurzatmigkeit bis Ruhedyspnoe, Brustschm., Fieber, Hypoxämie u. Infiltration im Thorax-Röntgenbild (cave ggf. Ther. sofort abbrechen). Exantheme, Erytheme, Juckreiz, Kopfschm., Müdigkeit, Benommenheit, Parästhesie. *Gelegentl.:* Herpes zoster, maligne Lymphome (z.T. reversibel), Panzytopenie, Agranulozytose, Stör. d. Hämatopoese, schw. allerg. Reakt. bis zum anaphylakt. Schock, diabet. Stoffwechsellaage, gastrointest. Ulzerationen u. Blutungen, Pankreatitis, Zystitis m. Ulzerationen (evtl. m. Hämaturie), Dysurie, Leberverfettung, chron. Leberfibrose u. -zirrhose, Abfall des Serumalbumins, Lungenfibrose, Pleuraerguss, Urtikaria, Photosensibilität, verstärkte Pigmentierung d. Haut, Haarausfall, Nodulosis, schmerzhaft Erosionen v. psoriatis. Plaque; als schwere

Enbrel®. Wirkstoff: Etanercept. **Zusammensetzung:** Enbrel 10 mg Pulv. u. Lsg.-mittel z. Herst. einer Inj.-Lsg. z. Anw. b. Kdrn. u. Jugendl., Enbrel 25 mg Pulv. u. Lsg.-mittel z. Herst. einer Inj.-Lsg. 1 Durchstechfl. enth. 10 mg bzw. 25 mg Etanercept. **Sonst. Bestandt.:** Pulv.: Mannitol, Saccharose, Trometamol. Lsg.-mittel: Wasser f. Inj.-Zwecke. Enbrel 25 mg u. 50 mg Inj.-Lsg. in Fertigspr. Enbrel 50 mg Inj.-Lsg. im Fertigpen (MYCLIC) 1 Fertigspr. enth. 25 mg bzw. 50 mg Etanercept, 1 Fertigen enth. 50 mg Etanercept. **Sonst. Bestandt.:** Saccharose, Natriumchlorid, Argininhydrochlorid, Natriumdihydrogenphosphat-Dihydrat, Natriummonohydrogenphosphat-Dihydrat, Wasser f. Inj.-Zwecke. Etanercept wird gentechn. aus der Eierstockszelllinie d. Chinesischen Hamsters hergestellt. **Anwendungsgebiete:** Enbrel 25 mg u. 50 mg: Rheumatoide Arthritis: in Komb. m. Methotrexat (MTX) z. Behandl. d. mittelschweren bis schweren aktiven rheumatoiden Arthritis (RA) b. Erw., wenn d. Ansprechen auf Basistherapeutika (einschl. MTX – sofern nicht kontraind.) unzureichend ist, Enbrel kann im Falle von MTX-Unverträglichk. od. wenn Forts. d. MTX-Behandl. nicht mögl. ist, als Monother. angewendet werden. Behandl. der schweren, aktiven u. progressiven RA 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 Gelenkschädigung u. verbessert d. körperl. Funktionsfähigk. **Psoriasis-Arthritis (Arthritis psoriatica):** Behandl. d. aktiven u. progressiven Psoriasis-Arthritis b. 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 Schädigung peripherer Gelenke b. Pat. m. polyartikulären symmetrischen Subtypen d. Erkrank. **Axiale Spondyloarthritis: Morbus Bechterew (ankylosierende Spondylitis):** Behandl. d. schweren aktiven Morbus Bechterew bei Erw., die unzureichend auf konventionelle Behandl. angesprochen haben. **Nicht-röntgenolog. axiale Spondyloarthritis (nr-AxSpa):** Behandl. Erw. m. schwerer nr-AxSpa, m. objektiven, durch erhöhtes CRP und/oder MRT nachgewies. Anzeichen. einer Entzünd., die unzureichend auf eine Behandl. m. NSARs angespr. haben. **Plaque-Psoriasis:** Behandl. Erwachsener m. mittelschwerer bis schwerer Plaque-Psoriasis, die auf eine andere system. Ther. wie Ciclosporin, MTX od. 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. Polyarthritiden (Rheumafaktor-positiv od. -negativ) u. d. erweiterten (extended) Oligoarthritiden bei Kdrn. u. Jugendl. ab 2 J., die unzureichend auf MTX-Behandl. angesprochen haben od. MTX-Behandl. nicht vertragen. Behandl. d. Psoriasis-Arthritis (Arthritis psoriatica) b. Jugendl. ab 12 J., die unzureichend auf MTX-Behandl. angesprochen haben od. MTX-Behandl. nicht vertragen. Behandl. d. Enthesitis-assoziierten Arthritis b. Jugendl. ab 12 J., die unzureichend auf eine konventionelle Ther. angesprochen haben od. eine konventionelle Ther. nicht vertragen. **Plaque-Psoriasis bei Kdrn. u. Jugendl.:** Behandl. d. chron. schweren Plaque-Psoriasis bei Kdrn. 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. Bestandt., Sepsis od. Risiko einer Sepsis, aktive Infekt., einschl. chron. od. lokalis. Infekt., Schwangerschaft, Stillzeit. **Nebenwirkungen:** Basierend auf Beobachtungen aus klin. Studien bei Erw. u. Berichten n. Markteinf.: *Sehr häufig:* Reakt. an d. Inj.-stelle, ggf. passage, „Recall“-Reakt. an d. Inj.-stelle, Infekt. (einschl. Infekt. d. oberen Atemwege, Bronchi-

tox. Erschein.: herpetiforme Hauteruptionen, Stevens-Johnson-Syndr., tox. epidermale Nekrolyse (Lyell-Syndr.), Vaskulitis (als schw. tox. Erscheinung), Depressionen, Hemiparese, Schwindel, Verwirrtheit, Krampfanfälle, Leukenzephalopathie/Enzephalopathie (bei parenteraler Anw.), fetale Missbildungen, vaginale Entzünd. u. Ulzerationen, Arthralgie, Maligne Osteoporose. *Selten:* Sepsis, megaloblastäre Anämie, Enteritis, Melaena, Gingivitis, Azotämie, akute Hepatitis u. Hepatotox., Pharyngitis, Atemstillstand, verstärkte Pigmentierung d. Nägel, Akne, Petechien, Ekchymosen, Erythema multiforme, erythematöse Hautausschläge, thromboembol. Ereignisse (einschl. arterieller u. zerebraler Thrombose, Thrombophlebitis, tiefe Venenthrombose, Retina-Venenthrombose, Lungenembolie), Stimmungschwank., vorübergehende Wahrnehmungsstör., Parese, Sprachstör. einschl. Dysarthrie u. Aphasie, Leukenzephalopathie (bei oraler Anw.), Sehstör. (verschommenes Sehen, Schleiersehen), schwerwieg. Sehstör. v. unbek. Ätiologie, Hypotonie, Abort, Oligospermie, Menstruationsstör., Belastungsfraktur. *Sehr selten:* Herpes-simplex-Hepatitis, schwere Verläufe von Knochenmarkdepression, aplastische Anämie, Hypogammaglobulinämie, Hämatemesis, akute Lebernekrose, Pneumocystis carinii-Pneumonie, Luftnot, Asthma bronchiale, chron. obstruktive Lungenerkrank., akute Paronychie, Furunkulose, Teleangiectasie, Muskelschwäche, Schmerzen i. d. Extremitäten, Geschmacksveränd. (metallischer Geschmack), Meningismus (Lähmungen, Erbrechen), akute asept. Meningitis, Konjunktivitis, Perikarditis, Perikardtamponade, Perikarderguss, fetaler Tod, gestörte Oogenese, Spermatogenese, Libidoverlust, Impotenz, Unfruchtbarkeit, Scheidenausfluss. *Häufigkeit nicht bekannt:* opportunist. Infekt. (teilw. letal), tödl. verlaufende Sepsis, Narkardiose, Histoplasma- u. Cryptococcus-Mykosen, disseminierter Herpes simplex u. durch Zytomegalievirus hervorgerufene Infekt. einschl. Pneumonie; Reaktivierung v. Hepatitis-B-Infekt., Verschleht. v. Hepatitis-C-Infekt., Lymphadenopathie, lymphoproliferative Erkrank., z.T. reversibel, Eosinophilie u. Neutropenie, allerg. Vaskulitis, Fieber (bedarf Abklärung gegenüber bakterieller od. mykot. Septikämie), Immunsuppr., nichtinfektiöse Peritonitis, Proteinurie, Herpes-simplex-Hepatitis, Leberinsuff., Wundheilungsstör.; -zusätzl. NW, die bei der i. d. R. höher dosierten onkolog. Anw. beobachtet wurden: Gelegentl. schwere Nephropathie od. Nierenversagen, sehr selten ungewöhnl. Sinneswahrnehm. od. vorübergehende Erblindung/Sehverlust. -zusätzl. -Fertigspr.: An d. Inj.-Stelle (i.m. Anw.) lokale Nebenw. (brennendes Gefühl) od. Gewebeschäden (sterile Abszessbildung, Untergang v. Fettgewebe). Bei s. c. Anw. bisher nur milde lokale Hautreakt. Bei i. v. Anw. akute Enzephalitis u. akute Enzephalopathie m. Todesfolge mögl. **Warnhinweise:** Die Einnahme bzw. Injektion v. Lantarel erfolgt 1x wöchentlich! Lantarel FS: Enth. Natrium < 1mmol (23 mg) pro FS. Lantarel Tbl.: Enth. Lactose. Weitere Informationen s. Fach- u. Gebrauchsinformation. **Abgabestatus:** Verschreibungspflichtig. **Pharmazeutischer Unternehmer:** PFIZER PHARMA GmbH, Linkstr. 10, 10785 Berlin. **Stand:** Januar 2014

tis, 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 Lungenerkrank. (einschl. pulmonale Fibrose u. Pneumonitis, z.T. letal), Angioödem, Urtikaria, Hautausschlag, psoriasisartiger Hautausschlag, Psoriasis (einschl. Erstmanifestationen od. Verschleht. u. pustulöse Formen, primär Handflächen u. Fußsohlen). *Selten:* Tuberkulose (inkl. Miliartuberkulose u. extrapulmonärer Tuberkulose), opportunist. Infekt. (einschl. invasive Pilz-, Protozoen-, Bakterien-, atypische Mykobakterien- und Virusinfekt. sowie Legionellose), Lymphom, Melanom, Anämie, Leukozytopenie, Neutropenie, Panzytopenie, schwere allerg./anaphylakt. Reakt. (einschl. Angioödem, Bronchospasmus), Sarkoidose, Anfälle, entmyelinisierende Prozesse des ZNS m. Verdacht auf multiple Sklerose od. lokalisierte entmyelinisierende Zustände wie Neuritis nervi optici u. Querschnittsmyelitis; Verschleht. v. kongest. Herzinsuff., erhöhte Leberenzyme, Autoimmunhepatitis, kutane Vaskulitis (einschl. leukozytoklastische Vaskulitis), Stevens-Johnson-Syndrom, Erythema multiforme, subakuter kutaner od. diskoider Lupus erythematodes, Lupus-ähn. Syndrom. *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, Merkelzellkarzinom, Makrophagenaktivierungssyndrom, Verschleht. einer Dermatomyositis. In Studien zur RA (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 u. 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. Bauchschmerzen. Es gab Berichte über chron.-entzündl. Darmerkrank.; Schwerw. NW umfassten: Varizellen-Infektion m. Zeichen u. Sympt. v. septischer Meningitis (ohne Folgeschäden), Blinddarmentz., Gastroenteritis, Depression/Persönlichkeitsstör., Hautgeschwür, Ösophagitis, Gastritis, sept. Schock, Typ 1 Diabetes mellitus, Weichteilinfekt. u. postoperative Wundinfekt. Weitere Informationen s. Fach- u. Gebrauchsinformation. **Abgabestatus:** Verschreibungspflichtig. **Pharmazeutischer Unternehmer:** Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, Vereinigtes Königreich. **Repräsentant in Deutschland:** PFIZER PHARMA GmbH, Linkstr. 10, 10785 Berlin. **Stand:** September 2014