Osteodensitometry showed osteoporosis. Oral methotrexate (MTX) 25 mg weekly for 3 months was initiated, and salazopyrin 1.5 g bid and hydroxychloroquin 200 mg qd were added in the following 3 months without attenuation of the frequency or severity of the attacks or allowing the prednisolone dose to be tapered. He suffered from chronic airway colonization with mucoid and non-mucoid Pseudomonas strains. Ten years earlier, he had been treated for a pulmonary non-tuberculosis mycobacterial (NTM) infection. Prior to etanercept treatment, sputum samples were repeatedly microscopy negative for mycobacteria. Because of the bacterial overgrowth, cultures were inconclusive, a frequent problem in CF patients. He had a normal chest X-ray. The QuantiFERON Gold-TB® test (Cellestis, Australia) and screening for hepatitis B and C were negative. We assessed that the risk of latent infection was minimal, and he started etanercept subcutaneously 50 mg weekly combined with MTX 25 mg weekly. In the first 3 months, arthralgia and clinical signs of synovitis resolved in both ankles and the left knee with minimal residual painless swelling of the right knee. US of the right knee revealed a thickened synovial membrane but no increased intra-articular fluid or Doppler activity. The Disease Activity Score based on CRP (DAS28-CRP) fell from 3.2 to 2.6 and the Clinical Disease Activity Index (CDAI) from 14.1 to 5.0. The CRP level remained normal during the etanercept treatment. Prednisolone was tapered to 2.5 mg daily. In the first 6 months, he had only one minor attack. His physical function improved significantly, and his Health Assessment Questionnaire (HAQ) score decreased from 1.0 to 0.375. He was able to start physical therapy and increase daily activities. He received planned intravenous anti-pseudomonas treatment quarterly, and no extra prednisolone, prevented complications, and provided a much higher quality of life.

Overall, this case demonstrates the efficacy and safety of TNF inhibition and supports early intensive immunosuppression in selected CF patients to control severe inflammatory comorbidities.

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Search for a concentration–effect curve of adalimumab in ankylosing spondylitis patients

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The immunogenicity of adalimumab is associated with decreased drug levels, resulting in loss of clinical response in rheumatoid arthritis (RA), psoriatic arthritis (PsA), psoriasis, and ankylosing spondylitis (AS) patients (1–5); however, in AS contradictory results have been published (6). A concentration–effect curve was previously identified in adalimumab-treated RA, PsA, and psoriasis patients with active disease, in which a therapeutic target drug level range was found between 3.5 mg/L and 8 mL/L approximately. (3, 7, 8), suggesting that tumour necrosis factor (TNF) is adequately blocked with adalimumab concentrations within this range. The aim of the current study was to determine a concentration–effect curve in AS patients treated with a standard dose of adalimumab and to identify a therapeutic concentration range at 24 weeks of treatment. Examining the therapeutic target range for AS might help to identify patients who are currently being undertreated or overtreated, and thus are eligible for treatment optimization.

In patients of the prospective observational AS adalimumab cohorts of Amsterdam (n = 74) and Taichung (n = 28), clinical data and samples were collected at baseline and at weeks 4, 12, and 24, and adalimumab trough concentrations (further referred to as ‘concentrations’) were measured retrospectively. Adalimumab concentration and anti-drug antibody (ADA) measurements have been described previously (1, 2). Disease activity was assessed using the Bath AS Disease Activity Index (BASDAI) (9) and the AS Disease Activity Score (ASDAS) using C-reactive protein (CRP) (10). To establish a concentration–effect curve at week 24, patients were sorted from low to high adalimumab concentrations with correlating ΔBASDAI (n = 102) and ΔASDAS (n = 91), as described previously (7). Response to adalimumab was determined using ΔBASDAI and ΔASDAS between baseline and 24 weeks of treatment and analysed using Spearman’s rank correlation coefficient. For differences in subpopulations, the Mann–Whitney U test or the χ² test was used, as appropriate. In patients discontinuing adalimumab treatment prematurely, the last observation carried forward (LOCF) approach was used. Statistical analyses were performed using SPSS version 21.0 (SPSS Inc, Chicago, IL, USA) and GraphPad Prism 5. A p-value < 0.05 was considered significant. The study was approved by the Medical Ethics Committee of both institutes. All patients gave written informed consent.

Of the 115 eligible patients, 102 (89%) enrolled in this study and 13 were excluded because of missing data. All 102 patients completed the BASDAI at baseline and at 24 weeks of follow-up, and for 91 patients (89%) an ASDAS could be calculated. Baseline characteristics (Table 1) show that the Taiwanese patients had more severe and longstanding disease than those in The Netherlands. Adalimumab concentrations at 24 weeks varied between 0 mg/L and 34.8 mg/L. Forty-seven patients (52%) showed a clinically relevant decrease of ≥ 1.1 in ASDAS at week 24 (10). A BASDAI decrease of ≥ 2.0 was present in 37 patients (36%). Figure 1 shows the

Table 1. Patient characteristics at baseline*.

| Demographics                       | Total population (n = 102) | The Netherlands (n = 74) | Taiwan (n = 28) | p value |
|------------------------------------|---------------------------|--------------------------|-----------------|---------|
| **Demographics**                   |                           |                          |                 |         |
| Age (years)                        | 42 ± 11                    | 43.6 ± 10.5              | 37.6 ± 12       | 0.02    |
| Male                               | 68 (67)                    | 44 (60)                  | 24 (86)         | 0.02    |
| BMI (kg/m²)                        | 24.8 (22.7–27.6)           | 24.5 (22.8–27.6)         | 25.0 (22.5–27.7)| 0.94    |
| **Disease status**                 |                           |                          |                 |         |
| Disease duration (years)           | 7.0 (2.0 – 15.5)           | 6.0 (1.0 – 14.0)         | 12.0 (6.0 – 17.8)| 0.02    |
| HLA-B27 positive                   | 85 (83.3)                  | 57 (77.0)                | 28 (100.0)      | 0.005   |
| CRP (mg/L)                         | 8.0 (3.0 – 17.0)           | 4.0 (2.5 – 12.5)         | 15.3 (10.9 – 25.7)| <0.001 |
| ESR (mm/h)                         | 22.0 (8.0 – 39.0)          | 14.0 (6.5 – 28.5)        | 38.0 (31.0 – 53.5)| <0.001 |
| ASDAS CRP                          | 3.4 ± 1.0                  | 3.1 (2.4 – 3.7)          | 4.2 (3.6 – 4.7) | <0.001  |
| BASDAI                             | 6.2 (4.4 – 7.5)            | 5.6 (3.9 – 7.1)          | 7.4 (6.5 – 8.0) | <0.001  |
| GDA VAS                            | 7.0 (5.0 – 8.0)            | 6.0 (4.0 – 8.0)          | 7.0 (5.3 – 8.0) | 0.12    |
| BASFI                              | 5.1 ± 2.5                  | 4.5 ± 2.5                | 6.5 ± 2.2       | <0.001  |
| **DMARD therapy**                  |                           |                          |                 |         |
| Prior biologicals                  | 18 (17.6)                  | 18 (24.3)                | 0 (0.0)         | 0.003   |
| Methotrexate use                   | 6 (5.9)                    | 6 (8.1)                  | 0 (0.0)         | 0.184   |
| Sulfasalazine use                  | 32 (31.4)                  | 7 (9.5)                  | 25 (89.3)       | <0.001  |
| NSAID use                          | 77 (75.5)                  | 49 (66.2)                | 28 (100.0)      | <0.001  |

BMI, Body mass index; HLA-B27, human leucocyte antigen B27; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; GDA VAS, general disease activity on a visual analogue scale (0–10); BASFI, Bath Ankylosing Spondylitis Functional Index; DMARD, disease-modifying anti-rheumatic drug; NSAID, non-steroidal anti-inflammatory drug.

*A similar table was previously published by Kneepkens et al (1).

1Disease duration since diagnosis.

Values given as mean ± standard deviation, median (interquartile range), or number (percentage).
The relationship between adalimumab concentration and clinical response. No significant correlation between adalimumab concentration at 24 weeks and ΔASDAS or ΔBASDAI was found. Concentration–effect curves in which adalimumab concentration was plotted against CRP, erythrocyte sedimentation rate (ESR), patient global and physician global assessment at week 24, and for patients with low (< 10 mg/L) vs. high (≥ 10 mg/L) CRP separately, could also not identify an adalimumab cut-off (data in supplementary file). The median (interquartile) drug level in patients with low CRP was significantly higher than in patients with high CRP at baseline [respectively 10.6 (3.9 – 16.2) vs. 6.9 (1.0 – 12.6); p = 0.019]. In 11 patients adalimumab was undetectable, and in 10 of these patients ADA was detectable with the assay used. In significantly more patients with high CRP, an ADA titre > 100 AU/mL was detected (4.8% vs. 3.4%; p = 0.04), irrespective of nationality.

In conclusion, to optimize adalimumab treatment in a personalized manner it is important to identify the therapeutic drug level range of adalimumab for each disease. The present study, however, could not establish this range for adalimumab in AS. This finding is inconsistent with findings in PsA and psoriasis, which have demonstrated clear concentration–effect relationships. Possible explanations might be that, in AS, as opposed to PsA and psoriasis, little target (TNF) is present, requiring only a small amount of adalimumab necessary for maximal target blockage. Hypothetically, a proportion of non-responding patients might experience non-TNF-driven disease and therefore influence results. Moreover, validated but mostly patient-reported outcome measurements we use for assessing disease activity (i.e. BASDAI and ASDAS) might not be a good representation of active inflammation directed by the TNF pathway.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplementary Figure 1: Concentration–effect curves.

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Scleroderma and liver disease: a case of an association with primary sclerosing cholangitis

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Scleroderma is a connective tissue disease reported more frequently in women than men. Dysregulation of the immune system and endothelial and fibroblast dysfunction are important pathogenetic mechanisms (1). Limited cutaneous (lcSc) and diffuse cutaneous (dcSc) forms of scleroderma are currently recognized. In lcSc, skin sclerosis is localized to the face, hands, and feet, and late visceral organ involvement and a strong association with anticientromere antibody (ACA) positivity are described. In dcSc, anti-topoisomerase I (Scl-70) antibodies are the hallmarks of the disease and skin fibrosis progresses from the limbs to the trunk with earlier visceral involvement, especially of the lungs, kidneys, and upper gastrointestinal tract (2). Liver disease is an uncommon feature of scleroderma. Approximately one-quarter of scleroderma patients are positive to antimitochondrial antibody (AMA), the serological hallmark of primary biliary cirrhosis (PBC), but only a few women, usually with localized scleroderma, develop PBC. (3).

A 79-year-old man was admitted for severe pruritus, cough, and dyspnea. He had suffered from oesophagitis and hiatal hernia and reported Raynaud’s phenomenon for 5 years. A recent liver ultrasound showed hepatomegaly without focal lesions. He denied smoking, alcohol consumption, drug intake, or exposure to toxic substances. On examination, scratched lesions on the body, telangiectasias on the face, and bilateral hand oedema were noted; expiratory wheezing and crackles on the right pulmonary base, and liver 2 cm enlarged with a palpable spleen but no swollen lymph nodes were remarked. Routine laboratory blood tests were all normal except for alanine aminotransferase (ALT) (67 U/L) and aspartate aminotransferase (57 U/L), alkaline phosphatase (479 U/L), and γ-glutamyl transferase (268 U/L). Biliary salts were raised (12.9 Umol/L), with normal bilirubin and negative viral hepatitis markers. Autoimmune profile (ANA, AMA, p-ANCA, c-ANCA, anti-LKM, ASMA, Scl70, RF, ACA) found ACA positive at 1:160. A chest X-ray showed ‘ground glass’ parenchyma and computed tomography (CT) confirmed interstitial fibrosis. A transthoracic echocardiogram revealed biastral enlargement, pulmonary hypertension (30 mmHg), and a left ventricular ejection fraction of 63%. Magnetic resonance (MR) of the biliary tract excluded hepatic duct strictures. Nailfold capillaroscopy displayed evident abnormalities (Figure 1A). On discharge, ursodeoxycholic acid 900 mg a day and pentoxiphilline 400 mg twice a day were prescribed, inducing normalization of the laboratory tests and rapid improvement of symptoms. Seven months later, after voluntarily stopping the treatment, the patient complained of the recurrence of a severe itch. Liver enzymes were still elevated (ALT 62 U/L; alkaline phosphatase 541 U/L; γ-glutamyl transferase 419 U/L). A liver biopsy showed alterations as illustrated in Figures 1B and 1C.

Primary sclerosing cholangitis (PSC) is a cholestatic disease that affects young and middle-aged men. Patients with PSC usually complain of pruritus and...