[3] Matucci-Cerinic M, Kahaleh B, Wigley FM. Review: evidence that systemic sclerosis is a vascular disease. Arthritis and rheumatism 2013; 65(8):1953–62.
[4] Pattanaik D, Brown M, Postlethwaite BC, Postlethwaite AE. Pathogenesis of Systemic Sclerosis. Frontiers in immunology 2015; 6:272.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.3739

THURSDAY, 15 JUNE 2017

Cytokines and chemokines

OP0097 SYSTEMIC IFN TYPE I AND TYPE II SIGNATURES IN PRIMARY SJÖGREN'S SYNDROME REVEAL DIFFERENCES IN DISEASE SEVERITY

I. Bodewes[1], S. Al-Ali[2,3], C.G. van Helden[1], N.I. Maria[1], J. Tarn[2], D. Lendrem[2], M.W. Schreurs[1], E.C. Steenwijk[1], P.L.A. van Daele[1,4], T. Both[4], S. Bowman[5], B. Griffiths[6], W.-F. Ng[2,7], M.A. Versnel[1]. *[1]Immunology, Erasmus MC, Rotterdam, Netherlands; [2]Musculoskeletal Research group, Newcastle University, Newcastle upon Tyne, United Kingdom; [3]University of Basrah, Basrah, Iraq; [4]Internal Medicine, Erasmus MC, Rotterdam, Netherlands; [5]Rheumatology, University Hospital Birmingham, Birmingham; [6]Newcastle upon Tyne Hospitals NHS Foundation Trust; [7]National Institute for Health Research, Newcastle Biomedical Research Centre, Newcastle upon Tyne, United Kingdom*

Background: Local and systemic activation of interferons (IFNs) has been demonstrated in primary Sjögren's syndrome (pSS).[1–4] Type I IFNs are associated with higher disease activity and autoantibody levels.[5] Recent findings also show activation of interferon type II (IFNγ) induced gene expression in salivary glands of pSS patients.[6, 7] Although IFN type I and II bind to different receptors they induce partially overlapping gene expression patterns. Understanding the relative contribution of IFN type I and type II may deepen our knowledge in pSS pathogenesis and promote a stratified approach to therapeutic development.
Objectives: Determine IFN type I and II inducible gene expression in patients with pSS and correlate this to disease manifestations.
Methods: In whole blood of 50 pSS patients modular IFN scores were determined using real-time quantitative PCR followed by principal component analysis. Subsequently, five indicator genes per module were analysed in two independent European cohorts with a total of 141 patients.
Results: Three groups were distinguished: without IFN activation (19–47%), with IFN type I (53–81%) and with IFN type I+II activation (35–55%). Patients with IFN activation (I or I+II) have a higher presence of auto-antibodies, IgG levels and lower lymphocyte counts compared to IFN negative patients. The biological domain of the EULAR Sjögren's Syndrome Disease Activity Index (biological-ESSDAI) was higher in patients with IFN activation, while total-ESSDAI scores were not significantly different.
66–67% of the IFN type I positive patients had an additional IFN type II inducible gene expression. Patients with IFN type I+II activation have significantly higher IgG levels and lower lymphocyte counts compared to patients with only IFN type I activation. There were no differences in fatigue or dryness, but pain scores were lower.
Conclusions: pSS patients can be stratified according to their systemic IFN activation patterns. IFN activation (I or I+II) is present in patients with the highest activity of the biological-ESSDAI. These data raise the possibility that the biological-ESSDAI rather than total-ESSDAI score may be a more sensitive endpoint for trials targeting either type I or type II IFN pathways.
References:
[1] Wildenberg, et al. EJI. 2008; 38(7):2024–2033.
[2] Gottenberg, et al. PNAS. 2006; 103(8):2770–2775.
[3] Hjelmervik, et al. A&R. 2005; 52(5):1534–1544.
[4] Emamian, et al. Genes Immun. 2009; 10(4):285–296.
[5] Brkic, et al. ARD. 2013; 72(5):728–735.
[6] Hall, et al. PNAS. 2013; 72(5):728–735.
[7] Hall, et al. A&R. 2012; 109(43):17609–17614.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.3688

THURSDAY, 15 JUNE 2017

Progress in biological treatment of RA

OP0098 REMISSION AND MAINTENANCE OF EFFICACY IN A PHASE 2B STUDY OF VOBARILIZUMAB, AN ANTI-INTERLEUKIN 6 RECEPTOR NANOBODY, IN PATIENTS WITH MODERATE-TO-SEVERE RHEUMATOID ARTHRITIS DESPITE TREATMENT WITH METHOTREXATE

T. Dörner[1], M. Weinblatt[2], P. Durez[3], R. Alten[4], K. Van Beneden[5], E.J. Dombrecht[5], K. De Beuf[5], P. Schoen[5], R.K. Zeldin[5]. *[1]Rheumatology and Clinical Immunology, Charité University Hospitals, Berlin, Germany; [2]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, United States; [3]Department Rheumatology, Cliniques Universitaires St-Luc, Sint-Lambrechts-Woluwe, Belgium; [4]Schlosspark-Klinik, Berlin, Germany; [5]Ablynx NV, Zwijnaarde, Belgium*

Background: Vobarilizumab is a Nanobody® consisting of an anti-IL-6R domain and an anti-human serum albumin domain in development for treatment of RA. The efficacy and safety were assessed in a 24-week double-blind global phase 2b study in patients with active RA on a stable background of MTX. Main efficacy and safety results were previously reported [1].
Objectives: To report the impact of treatment with vobarilizumab on secondary efficacy endpoints including SDAI and CDAI remission and the sustained response at 4 consecutive visits based on ACR50, ACR70 and $DAS28_{CRP}$.
Methods: Patients were randomized to receive subcutaneously administered placebo or 1 of 4 dose regimens of vobarilizumab in addition to MTX. SDAI and CDAI remission at Week 24 was evaluated, as was maintenance of efficacy as defined by sustained $DAS28_{CRP} < 2.6$ responses at 4 consecutive visits (i.e., at Weeks 12, 16, 20 and 24). In addition, a post-hoc analysis was performed on sustained ACR50 and ACR70 responses from Week 12 through Week 24. Proportions of patients achieving response for these endpoints were summarized by treatment group. Subjects with missing values were analyzed as non-responders.
Results: A total of 345 patients were randomized. Demographics and baseline characteristics were similar across groups with mean baseline $DAS28_{CRP}$ between 5.8 and 6.2. At Week 24, up to 19% and 20% in the vobarilizumab groups reached CDAI and SDAI remission, respectively vs. 10% and 9% who received placebo (Table 1).

Table 1. Percentage of patients with CDAI and SDAI remission at Week 24

	Placebo (N=69)	Vobarilizumab 75mg q4w (N=69)	Vobarilizumab 150mg q4w (N=70)	Vobarilizumab 150mg q2w (N=68)	Vobarilizumab 225mg q2w (N=69)
CDAI remission (≤2.8)	10	15	19	12	19
SDAI remission (≤3.3)	9	10	19	15	20

At Week 24, up to 61% and 45% of the patients in the vobarilizumab groups achieved an ACR50 or ACR70 response, respectively (39% and 17% on placebo). Approximately one third of the randomized patients in the 3 highest treatment groups had a sustained ACR50 response from Week 12 through Week 24 (Table 2). Sustained remission defined by $DAS28_{CRP} < 2.6$ at 4 consecutive visits, i.e. at weeks 12, 16, 20 and 24, was observed in 20% to 25% of the patients in the 3 highest dosing arms compared with 3% of those receiving placebo.

Table 2. Percentage of patients with sustained efficacy response at 4 consecutive visits (Weeks 12, 16, 20 and 24)

	Placebo (N=69)	Vobarilizumab 75mg q4w (N=69)	Vobarilizumab 150mg q4w (N=70)	Vobarilizumab 150mg q2w (N=68)	Vobarilizumab 225mg q2w (N=69)
$DAS28_{CRP}$ <2.6	3	4	20	25	20
ACR50	16	14	29	31	39
ACR70	4	7	11	13	13

Conclusions: In patients with active RA, treatment with vobarilizumab at the 3 highest dose regimens in addition to MTX had a positive and sustained impact on disease activity through Week 24 as defined by clinically relevant efficacy endpoints.
References:
[1] Weinblatt et al. (Annual Scientific Meeting, Canadian Rheumatology Association, 2017).
Disclosure of Interest: T. Dörner Consultant for: Ablynx, M. Weinblatt Consultant for: Ablynx, P. Durez Consultant for: Ablynx, R. Alten Consultant for: Ablynx, K. Van Beneden Employee of: Ablynx, E. Dombrecht Employee of: Ablynx, K. De Beuf Employee of: Ablynx, P. Schoen Employee of: Ablynx, R. Zeldin Employee of: Ablynx
DOI: 10.1136/annrheumdis-2017-eular.3732

OP0099 SAFETY, TOLERABILITY AND INITIAL SIGNS OF EFFICACY OF THE FULLY HUMAN IMMUNOCYTOKINE DEKAVIL (F8IL10): A NOVEL THERAPEUTIC APPROACH FOR RHEUMATOID ARTHRITIS

M. Galeazzi[1], G. Sebastiani[2], R. Voll[3], J. Wollenhaupt[4], O. Viapiana[5], J. Dudler[6], E. Selvi[1], C. Baldi[1], M. Bardelli[1], B. Bannert[3], S. Finzel[3], C. Specker[7], P. Sarzi Puttini[8], F. Bootz[9], D. Neri[10] on behalf of the DEKAVIL Study Group. *[1]University Hospital, Siena; [2]San Camillo-Forlanini Hospital, Rome, Italy; [3]University Medical Center, Freiburg; [4]Schoen-Klinik, Hamburg Eilbek, Germany; [5]University Hospital, Verona, Italy; [6]Cantonal Hospital, Fribourg, Switzerland; [7]University Hospital, Essen, Germany; [8]Luigi Sacco Hospital, Milan, Italy; [9]Philochem AG, Otelfingen, Switzerland; [10]Philogen SpA, Siena, Italy*

Background: The antibody-based targeted pharmacodelivery of cytokines by means of immunocytokines has the potential to enhance therapeutic activity at the site of disease while sparing healthy tissues. Dekavil (F8IL10) is a fully human immunocytokine composed of the vascular targeting antibody F8 (specific to

EDA) fused to the cytokine interleukin-10. Dekavil is currently in phase II clinical development for the treatment of rheumatoid arthritis (RA).
Objectives: In the phase Ib dose escalation study, the primary objective was to explore safety, tolerability and the maximum tolerated dose of Dekavil when administered in combination with methotrexate (MTX). The aim of the currently ongoing phase II study is to assess therapeutic activity of Dekavil plus MTX over MTX alone by measuring the mean change from baseline of DAS28-CRP. Immunogenicity of F8IL10 and its PK and PD profile will also be explored.
Methods: Patients with active RA despite MTX therapy and who failed anti-TNF treatment are the target population of both studies. In the phase Ib trial, cohorts of 3–6 patients were treated with escalating doses of Dekavil (6, 15, 30, 60, 110, 160, 210, 300, 450 and 600 μg/kg) in combination with a fixed dose of MTX (10–15 mg). In the multicenter, double-blind, placebo-controlled phase 2 study, patients are randomized into two treatment groups (Dekavil 30 or 160 μg/kg plus MTX) and one placebo group (placebo plus MTX). Dekavil is administered once weekly by *s.c.* injection for a maximum of 8 weeks in both studies.
Results: Dekavil has been shown to be well tolerated up to the highest investigated dose (600 μg/kg) and an MTD was not reached. In 33 out of 34 patients treated in the phase 1 study, no DLTs, no SAEs and no SUSARs have been reported. One patient in cohort 9 (450 μg/kg) experienced a DLT (G2 purpura) and a SAE (G2 dyspnea, not drug related). The patient received corticosteroids and fully recovered within one week. Mild injection site reactions were the most frequently observed adverse events and occurred in 62% of the patients. Furthermore, two cases of drug related anemia (G2 and G3) were reported in this study. All adverse reactions resolved completely. At the first efficacy assessment after 4 cycles of treatment, 48% of evaluable patients (16/33) revealed ACR and/or EULAR responses. The fraction of responding patients increased to 57.7% (15/26) after 8 cycles of treatment. Two patients benefited from ACR70 responses for more than 12 months after the last drug administration. As of January 2017, 22 out of 87 patients have been treated in the phase 2 clinical study and neither SUSAR nor treatment-related deaths were recorded.
Conclusions: The currently available data suggest that Dekavil is a safe and promising novel therapeutic for the treatments of RA.
Disclosure of Interest: M. Galeazzi: None declared, G. Sebastiani: None declared, R. Voll: None declared, J. Wollenhaupt: None declared, O. Viapiana: None declared, J. Dudler: None declared, E. Selvi: None declared, C. Baldi: None declared, M. Bardelli: None declared, B. Bannert: None declared, S. Finzel: None declared, C. Specker: None declared, P. Sarzi Puttini: None declared, F. Bootz Employee of: Philochem AG, D. Neri Shareholder of: Philogen SpA
DOI: 10.1136/annrheumdis-2017-eular.4840

OP0100 OVERALL CANCER RISK IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH TNF INHIBITORS, TOCILIZUMAB, ABATACEPT, OR RITUXIMAB

H. Wadström, T. Frisell, J. Askling on behalf of The ARTIS study group.
Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden

Background: Immune incompetence may lower host surveillance against incipient tumours. Conversely, immune therapies have emerged as a promising therapeutic approach to cancer. Malignancies thus constitute an important aspect of the safety of biologics as used in Rheumatology, including agents targeting TNF, CD20 and IL6, and immunomodulation using CTLA4. Whereas previous reports concerning TNF inhibitors (TNFi) and risk of malignancies in rheumatoid arthritis (RA) have mostly been reassuring, risks with other biological disease modifying anti-rheumatic drugs (bDMARDs) are less studied.
Objectives: To assess the risk of malignancies in patients with RA treated with bDMARDs.
Methods: Through linkages of Swedish national and population-based registers we assembled cohorts of patients with RA initiating (Jan 2006 through Dec 2014) a first ever treatment of tocilizumab, abatacept, rituximab, or a TNFi, one cohort of patients initiating a second TNFi, one cohort of biologics-naïve csDMARD treated RA. Through linkage with the Swedish Cancer Register information on incident cancers was collected. Outcomes were defined as a first ever solid or hematologic malignancy excluding non-melanoma skin cancer (NMSC) during follow-up. Patients with a previous malignancy were excluded. Patients were followed from treatment start until death, emigration, outcome or end of follow up (Dec 2014). Hazard ratios were calculated using Cox-regression adjusted for age, sex, educational level, comorbidities, sero-positivity, number of hospitalizations and days spent in inpatient care, use of prednisolone at baseline, use of non-steroidal anti-inflammatory drugs (NSAIDs) at baseline, number of prescription drugs at baseline, and sick leave and disability (yes/no) the year before cohort entry.
Results: Adjusted for age, sex, disease- and treatment characteristics (see above), and educational level, there were no statistically significant differences in risk of a first solid or hematologic malignancy between initiators of tocilizumab, abatacept, rituximab, or a first- or second TNFi, and RA patients treated with csDMARDs.

Table 1. Number of persons, events, crude incidence, and hazard ratios for a first invasive solid or hematologic malignancy excluding NMSC

Outcome definition Cohort	Number of persons at risk	Number of events	Crude incidence per 10,000 pys	HR*
First invasive solid or hematologic malignancy excluding NMSC				
Tocilizumab	1408	30	80	0.78 (0.54–1.12)
Abatacept	1565	45	104	0.95 (0.70–1.28)
Rituximab	2793	108	103	0.86 (0.70–1.04)
First TNFi	9355	369	93	0.91 (0.82–1.01)
Second TNFi	3610	129	87	0.88 (0.73–1.05)
csDMARD RA	40071	2797	131	1 (reference)

*Adjusted for age, sex, disease- and treatment characteristics, and educational level.

Conclusions: The overall risk of malignancies among RA patients initiating, tocilizumab, abatacept, rituximab, or a first- or second TNFi in clinical practice did not differ substantially from that of RA patients treated with csDMARDs. Increased risk of tumours at specific sites, or with longer latency, cannot be excluded.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.4048

OP0101 RISK OF OPPORTUNISTIC INFECTIONS IN PATIENTS WITH RHEUMATOID ARTHRITIS INITIATING ABATACEPT: ANALYSIS OF ALL AVAILABLE CLINICAL TRIAL DATA

T. Simon[1], T. Gelarden[1], E. Nkhoma[1], M. Zhou[1], S. Banerjee[1], K. Winthrop[2].
[1]*Bristol-Myers Squibb, Princeton;* [2]*Oregon Health & Science University, Portland, United States*

Background: Opportunistic infections (OI) during treatment with abatacept (ABA) have been previously reported but are lacking a comprehensive analysis.
Objectives: To present the overall incidence rates of OI and herpes infections observed in patients (pts) receiving ABA using combined clinical trial data.
Methods: OI adverse events were summarized from 16 clinical trials (both placebo-controlled and cumulative abatacept exposure); all pts randomized to placebo were on a non-biologic DMARD. Incidence rates (per 100 person-years [p-y]) were calculated by the number of pts experiencing the first event divided by the total number of p-y of exposure. The p-y of exposure was censored at the time of the first event, death, discontinuation or end of study. Random effects meta-regression was performed across the trials to estimate the frequency of OI after adjusting for between-study heterogeneity. OI were identified using a pre-specified list in the setting of biologic therapy for patients with RA. Criteria for consideration were based on type, location of the infection and causing organism. Excluded from the list were non-specific infections caused by organisms considered to be opportunistic, but common in the general population.
Results: A total of 7044 pts with RA with ~21,330 p-y of ABA exposure were included in the cumulative randomized trial data (Table). The frequency of OI

Abstract OP0101 – Table 1

Infection Outcome	Abatacept (N=2653) p-y=2355		Placebo (N=1485) p-y=1253		Cumulative abatacept (N=7044) p-y=21,330	
	N (%)	IR/100 p-y (95% CI)	N (%)	IR/100 p-y (95% CI)	N (%)	IR/100 p-y (95% CI)
Opportunistic infections*	4 (0.2)	0.17 (0.05, 0.43)	7 (0.5)	0.56 (0.22, 1.15)	45 (0.6)†	0.21 (0.15, 0.28)†
Bronchopulmonary aspergillosis	1 (<0.1)	0.04 (0, 0.2)	0	0	2 (<0.1)	0.01 (0.00, 0.03)
Eye infection fungal	1 (<0.1)	0.04 (0, 0.2)	0	0	3 (<0.1)	0.01 (0.00, 0.04)
Gastrointestinal candidiasis	0	0	1 (<0.1)	0.08 (0, 0.4)	–	–
Fungal oesophagitis	0	0	1 (<0.1)	0.08 (0, 0.4)	1 (<0.1)	0.00 (0.00, 0.03)
Meningitis cryptococcal	0	0	1 (<0.1)	0.08 (0, 0.4)	–	–
Oesophageal candidiasis	0	0	1 (<0.1)	0.08 (0, 0.4)	7 (0.1)	0.03 (0.01, 0.07)
Pneumocystis jirovecii pneumonia	0	0	1 (<0.1)	0.08 (0, 0.4)	1 (<0.1)	0.00 (0.00, 0.03)
Pneumonia pseudomonal	1 (<0.1)	0.04 (0, 0.2)	0	0	1 (<0.1)	0.00 (0.00, 0.03)
Respiratory moniliasis	0	0	1 (<0.1)	0.08 (0, 0.4)	2 (<0.1)	0.01 (0.00, 0.03)
Tuberculosis	1 (<0.1)	0.04 (0, 0.2)	1 (0.1)	0.08 (0, 0.4)	17 (0.2)‡	0.08 (0.05, 0.13)‡
Herpes						
Herpes simplex	57 (2.1)	2.5 (1.9, 3.2)	22 (1.5)	1.8 (1.1, 2.7)	60 (0.9)	0.28 (0.22, 0.37)
Herpes zoster	44 (1.7)	1.9 (1.4, 2.5)	21 (1.4)	1.7 (1.1, 2.6)	284 (4)	1.38 (1.22, 1.55)
Herpes virus infection	5 (0.2)	0.2 (0.1, 0.5)	4 (0.3)	0.3 (0.1, 0.8)	–	–

*Except herpes; †n (%) for SAE was 19 and IR/100 p-y was 0.1 (95% CI 0.05, 0.14); ‡n (%) for SAE was 11 and IR/100 p-y was 0.05 (95% CI 0.03, 0.09); '–' indicates value is not available. SAE = serious AE.