EULAR 2017 Congress

Annual European Congress of Rheumatology

14-17 JUNE 2017 • MADRID • SPAIN

PEER-REVIEWED CONFERENCE REPORT

Surprise results for early high dose glucocorticoids in RA treatment

The addition of high-dose glucocorticoids to first-line adalimumab and methotrexate in the treatment of rheumatoid arthritis fails to further improve efficacy.

read more on PAGE 5

TNF inhibitors seem to reduce odds of radiographic progression in AS

Effect is mediated, at least in part, by a decrease in disease activity.

read more on PAGE 9

Scleroderma: long-term treatment

Rituximab, intended to depleted the B cell population, delays the onset of RA in high-risk patients.

read more on PAGE 21

MEDICOM MEDICAL PUBLISHERS

Editor Prof. dr. F.C. Breedveld, Leiden University Medical Centre, The Netherlands

Contents

COLOPHON

Editor	**Prof. dr. F.C. Breedveld** Leiden University Medical Center, NL
Advisory Board	Prof. dr. D. Poddubnyy Charité Universitätsmedizin, Germany
Editorial Manager	Lisa Colson
Editorial Co-ordinators	Nalinee Pathak, MSc. Bas Braakman, MSc.
Executive Publisher	Rene Draper, MSc.
Medical Writer	Constanace de Koning, LLM
Production Manager	Desiree Heijl
Graphic Design	MOOZ grafisch ontwerp
Lay Out	In het Houten Paard Wim Kempink

MEDICOM
MEDICAL PUBLISHERS

Postal address
Medicom Medical Publishers
PO Box 90
Zipcode 3740 AB
City Baarn
Country The Netherlands

Head Office
Medicom Medical Publishers
Faas Eliaslaan 5
3742 AR Baarn
The Netherlands

Telephone +31 85 4012 560
Fax +31 85 4012 569
E-mail publishers@medicom.nl

ISSN 2468-8762 17:11

Letter from the Editor

Prof. dr. F.C. (Ferry) Breedveld

Dear Reader,

It is a great pleasure to present a report on the 2017- EULAR-conference held in Madrid June 14-17. The meeting was attended by more than 14000 delegates who actively participated. The programme covered all aspects of rheumatology both explorative research and clinical studies. This report made a selection of the presentations that may be of most interest to the practicing clinicians. The conclusion is justified that the congress presented many new insights in the course and outcome of rheumatic diseases as well as many data on new treatment modalities as well as optimal forms on how to apply treatment options.

We hope that you enjoy our selections.

With Best Regards,

F.C. Breedveld

Biography

Professor Breedveld trained in Leiden University Medical Centre and Beth Israel Hospital in Boston. His major interest is the pathophysiology of rheumatoid arthritis and rational treatments. In 1989, he was appointed to the chair of rheumatology in Leiden. From 2005 to 2007 he served as president of EULAR. There he contributed with quality assurance in the treatment of autoimmune rheumatic diseases and in the further development of the annual conference.

Rheumatoid Arthritis: Development, Diagnosis and Prognosis

To date, a good few risk factors involved in the development of rheumatoid arthritis (RA) have been identified, followed by increasing evidence on new and different risk factors. More insights have been gathered on risks that may come with RA treatment and the role of comorbidities and early intervention in disease progression and remission. New data on different treatment options for RA holds interesting promises, especially with regard to specific subpopulations of patients.

Body fat/waist size linked to increased risk of developing RA in women

Women who are overweight or obese – defined by body mass index (BMI), abdominal obesity (waist circumference >88 cm) and a higher body fat percentage – have a higher risk of developing RA than those who are not. However, there is no clear association between the risk of RA and the different criteria that define being overweight or obesity in men. Hazard ratios (HR) were adjusted for potential confounding factors such as age, smoking status, total tobacco consumption, smoking duration, alcohol consumption, socio-economic status, physical activity (based on a formula that calculates the energy expenditure of different physical activities), and total intake of N-3 fatty acids (Table 1) [1].

These findings were derived from a population of 54,284 subjects, of which 52% was female, and aged between 50-64 years at the time of recruitment between 1993 and 1997. Of those subjects, 283 women and 110 men developed RA during a median follow-up period of 21 years. The median time to RA onset was 7 years [1].

Table 1 HR for developing RA in conjunction with BMI in women/men [1]

Factor	Women	Men
BMI 25-29.99 kg/m²	HR 1.48 (95% CI* 1.14-1.91)	HR 0.83 (95% CI 0.55-1.24)
BMI >30 kg/m²	HR 1.54 (95% CI 1.09-2.17)	HR 0.69 (95% CI 0.37-1.30)
Abdominal obesity (for women: waist circumference >88 cm; for men: waist circumference >102 cm)	HR 1.24 (95% CI 0.96-1.61)	HR 1.16 (95% CI 0.75-1.80)
For each 1% higher body fat percentage	HR 1.03 (95% CI 1.01-1.05)	HR 0.99 (95% CI 0.96-1.03)

*CI = confidence interval

Smoking: passive smoking in childhood associated with RA

Another risk factor contributing to the development of RA is passive smoking in childhood: this significantly increases the risk of RA in adult smokers. A total of 70,598 women with birth dates between 1925-1950 were prospectively followed since 1990. Of these, 1,239 patients self-reported developing RA; 350 of these cases were eligible for analysis concerning the link between active and passive smoking. The mean age at inclusion was 49.0 years and the mean duration of follow-up was 21.2 years. In smokers with passive exposure to smoke during childhood, the HR was 1.73 compared with non-smokers who were not exposed to smoke during childhood. Active smokers who had not been exposed to passive smoke during childhood had HR 1.37 [2].

Excess risk CV events decreased since start of 21st century

It is common knowledge that RA patients have an increased risk of cardiovascular disease (CVD) or cardiovascular (CV) events, including stroke, myocardial infarction (MI), congestive heart failure (CHF) and cardiovascular mortality (CVM) [3][4]. Although an analysis by Filhol et al. confirmed that RA patients harbour an increased risk of CVD compared to the general population, this excess risk appears to be less prevalent in the current era than prior to the year 2000. These findings were obtained by performing a detailed literature search. For studies published before 2000, a highly significant increase in the risk of all four CV events was observed in RA patients vs the controls (Table 2).

The researchers suggested two possible explanations for these findings: better management of CV risk in RA patients or better control of chronic systemic inflammation as a result of new therapeutic strategies with biologic disease-modifying anti-rheumatic drugs (DMARDs) [3][5][6].

Table 2 RR for CV events prior and after the year 2000 [5]

	RR before the year 2000	RR after the year 2000
Stroke	1.12 P=0.002	1.12 P=0.006
CHF	1.21 P<0.00001	1.17 P=0.27
CVM	1.25 P<0.00001	1.07 P=0.71
MI	1.32 P<0.00001	1.18 P<0.00001

Depression/anxiety may reduce likelihood of remission based on composite scores in RA

Michelsen et al. investigated the predictive value of baseline depression/anxiety on the likelihood of achieving remission in RA as well as the associations between baseline depression/anxiety and the components of the remission criteria at follow-up. RA patients starting first-time tumour necrosis factor (TNF)-inhibitors and DMARDs-naïve RA patients starting methotrexate between 2006-2012 from the prospective, multi-center NOR-DMARD study were included. This resulted in a total of 1,450 RA included patients. Patients had a mean age of 54.4 years, the median disease duration was 0.4 years, 28.6% were current smokers and 68.7% was female. According to the Short Form (SF)-36 Mental Health (MH)≤56/SF-36 Mental Component Summary score (MCS)≤38 criteria, 18.1%/29.9% of the patients were depressed/anxious at baseline. Lower percentages of patients with versus without baseline depression/anxiety achieved remission at 3 and 6 months treatment. Baseline depression/anxiety negatively predicted remission after 3 and 6 months. These findings were confirmed in separate subgroup analyses of TNF-inhibitor/methotrexate-treated patients. Baseline depression/anxiety were associated with increased patient's and evaluator's global assessment and 28 tender joint count at 3 and 6 months, but not with the level of acute phase reactants or 28 swollen joint count. Thus, depression and anxiety may reduce the likelihood of remission based on composite scores in RA and should be taken into account in individual patients when making a shared decision on a treatment target [7].

Early therapeutic intervention for Pre-RA patients significantly reduces RA risk

Early treatment of patients with 'pre-rheumathoid arthritis' – pre-RA, defined as undifferentiated arthritis or very early RA – significantly reduces the risk of the occurrence of RA in these patients at 52 weeks or more [8][9][10]. This was shown by a meta-analysis of 9 studies with a total of 1,156 patients. The mean age of the patients was 45.8 years and mean symptom duration 16.2 years. The occurrence of RA at week 52 was available in 6 studies; for week 120, data was derived from 1 additional study. In total, 800 patients were covered by these studies. Early therapeutic intervention in these pre-RA patients included methylprednisolone, methotrexate, TNF-blockers, abatacept or rituximab [11].

Table 3 Evolving TKR and THR rates <2002 and >2003 in RA patients [12]

	TKR per 1,000 person years	THR per 1,000 person years
Baseline incidence rate	5.87/1,000	8.72/1,000
<2002	+0.19 per year	-0.38 per year*
>2003	-0.20 per year	-0.83 per year

* In 2003, there was a temporary increase of +2.23 in THR incidence per year

Treatment

Less knee and hip replacements with bDMARDs guidelines

A Danish study investigated the number of total knee replacements (TKR) and total hip replacements (THR) in RA patients prior to and after national guidelines recommendations for biological (b)DMARD treatment for RA were introduced in Denmark in 2002. In this analysis, trends in the pre-bDMARD guideline era (1996-2002) were compared with those in the bDMARD period (2003-2016). The 5-year age and sex-standardised incidence rates (IR) of THR and TKR were calculated for 30,868 RA patients diagnosed between 1996-2011. These were compared with 301,527 matched (RA-free) controls. The incidence of TKRs carried out on RA patients started to decrease after the introduction of bDMARDs to national treatment guidelines. Prior to 2002 – when the new guidance was introduced – the incidence of TKR had been increasing among RA patients. In matched individuals, the incidence of TKR continued to increase throughout the entire study period (1996-2016). Contrarily, the incidence of TKR carried out on patients with RA started to decrease after the introduction of bDMARDs to national treatment guidelines. With regard to the incidence of THRs, it was clear that these also continued to steadily increase in the matched population. However, among RA patients – apart from a rather surprising increase in 2003 – the incidence of THR has followed an ongoing downward trend both after and before the guidance was introduced (Table 3).

The researchers noted that the observed findings are in line with a similar pattern recently reported in England and Wales [12].

No increased cancer risk bDMARDs

Recent data have shown that RA patients and a previous history of solid, non-skin cancer, who were treated with anti-TNF treatment did not experience any more cancer recurrences than RA patients treated with other classes of anti-rheumatic drugs. Moreover, the risk did not vary

depending on the timing of the start of anti-TNF treatment in relation to the original cancer diagnosis. A total of 446 patients with at least one diagnosis of solid cancer prior to the start of anti-TNF treatment were compared with 1,278 matched controls with a history of equally recent cancer. Both groups had a cancer recurrence of 7% (crude IR 14/1000 person years). Statistical analysis accounting for matching variables (sex, birth year, year of diagnosis of the index cancer and index cancer type and stage) as well as adjusting for education level and comorbidities indicated no increased risk associated with any specific cancer type apart from one possible exception. The HR for the recurrence of uterine cancer was 14.8, but this was based on just 1 event among the anti-TNF treated patients. The mean time from the index cancer diagnosis until the anti-TNF treatment/start of follow-up was 9.9 and 9.5 years among the anti-TNF treated patients and their matched biologic-naïve controls, respectively. The mean follow-up from the start of anti-TNF treatment was 4.9 and 4.1 years, respectively. The cancer stage distribution was similar between the two groups, apart from stage 4 (0.6 % among the anti-TNF treated patients and 1.6% among the biologic-naïve controls) [13].

Factors associated with treatment adherence

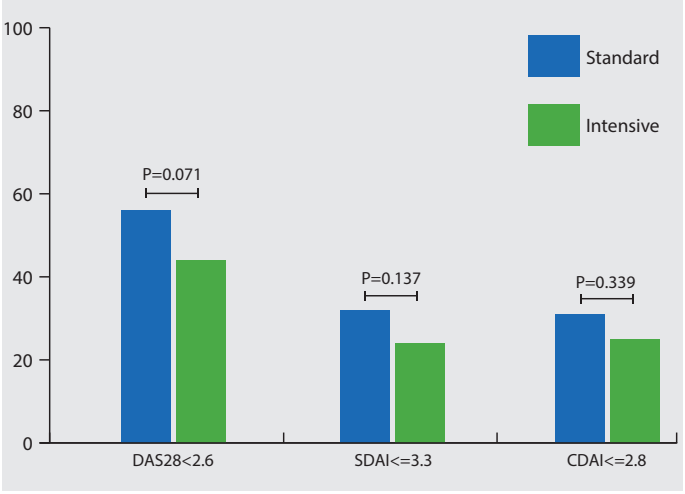
Non-adherence to treatment in RA has a negative impact on treat-to-target goals and disease outcomes. Goh et al. aimed to determine the factors associated with non-adherence in patients with RA by conducting an electronic literature search. A total of 75 papers was used of which 65 were based on observational studies and 10 on clinical trials. Factors associated with non-adherence were broadly categorized into patient-related factors (socio-demographic factors, patient perceptions [beliefs/knowledge/attitudes]), disease-related factors (disease duration/severity, comorbidities, functional disability) and treatment-related factors (drug type/method of administration/duration/regimen complexity, and combination therapy). It was found that 70% of all included studies reported significant associations between patient-driven factors and non-adherence. Adherence was found to be negatively associated with socioeconomic status, health literacy, and beliefs/perceptions/knowledge of RA and treatment. Moreover, poorer mental health state and greater disability/pain seem to be implicated in non-adherence as well. Although a few studies (N=3) reported a negative correlation, disease duration was largely non-significant in treatment adherence. Combining biologics with DMARDs was associated with improved adherence in patients. However, considering non-bDMARDs only, adherence rates were higher amongst monotherapy users. One study identified polypharmacy to be negatively associated with adherence and drug side effects were associated with non-adherence (N=7) [14].

Anti-TNF

Adalimumab: use in early, aggressive RA

In patients with early, aggressive RA, adalimumab combined with methotrexate has proven to be superior to either methotrexate or adalimumab alone in achieving clinical remission. It has also been demonstrated that short-term aggressive treatment with high-dose glucocorticoids plus conventional DMARDs is able to achieve long-term – up to 5 years – benefits. Caporali et al. compared the proportion of patients achieving remission at 12 months between two groups of subjects treated with adalimumab + methotrexate + high dose glucocorticoids (intensive, N=115) and adalimumab + methotrexate + placebo (standard, N=118). They also evaluated the number of patients maintaining remission at 24 months, after discontinuation of glucocorticoids at 6 months and discontinuation of adalimumab at 12 months. All subjects received adalimumab for 12 months and methotrexate (20 mg/w) to the end of month 24. Subjects were randomized to receive prednisone (orally, 50 mg/d, progressively tapered to 6.25 mg and stopped at month 6) or placebo. Patients were eligible if they had active RA, disease duration ≤1 year, and if they were glucocorticoid- and methotrexate-naïve. Remission rates (Disease Activity Score [DAS]28<2.6, Simplified Disease Activity Index [SDAI]≤3.3, Clinical Disease Activity Index [CDAI]≤2.8) at 1 year in the standard vs the intensive group were 56.25% vs 45.28%, 30.36% vs 21.69% and 28.57% vs 22.64%, respectively (Figure 1). At 2 years, DAS28 remission was 36.84% in the standard

Figure 1 Remission rates standard vs intensive treatment [15]



group vs 30.93% in the intensive group. No superiority of the intensive group was seen in the American College of Rheumatology (ACR)20, ACR50 and ACR70 response rates at 4, 8, 12, and 24 months. The overall frequency of adverse events (AEs) in patients who completed the trial was comparable between the groups. However, a higher percentage of patients discontinued due to AEs in the intensive group (16.52% vs 9.32%) [15].

Comparing effectiveness of different anti-TNF drugs as first bDMARD at 1 year

Turesson et al. compared the effectiveness of different TNF-inhibitors in a large, population-representative, sample of bio-naïve RA patients, based on the Swedish Rheumatology Quality register. This registry prospectively recorded clinical data of RA patients at treatment initiation and at subsequent visits. A total of 5,568 patients who initiated a TNF-inhibitor as their first ever bDMARD in 2010–2014 were included and followed through 2015. A significant difference in the adjusted chance of drug survival across TNF-inhibitors was apparent (Table 4).

RA patients who started with infliximab or certolizumab as their first biologic DMARD were less likely to remain on treatment compared to those started on etanercept. Patients initiating infliximab had a significantly lower chance of achieving each of the clinical response measures compared to patients treated with etanercept. No consistent differences in clinical effectiveness between etanercept and adalimumab or golimumab were observed. The researchers noted that the observed patterns may have been affected by treatment context [16].

Table 4 Status at the 1-year evaluation visit among patients with RA initiating a TNF-inhibitor as their first ever bDMARD [16]

	Etanercept N=1651	Infliximab n-1366	Adalimumab N=1004	Certolizumab n-921	Golimumab n-626	P
Observed Percentage						
On drug	70.6	66.4	69.2	65.2	68.0	
EULAR good response*	28.0	23.9	25.9	24.3	27.8	
DAS 28 remission*	25.9	21.3	26.0	22.4	27.7	
HAQ Improvement*	28.0	24.5	29.0	25.0	24.8	
28 joint counts = 0*	23.3	16.8	20.4	19.0	21.6	
Adjusted† relative risk (95% CI)						
On drug	Ref.	0.94 (0.89-1.00)	0.98 (0.92-1.04)	0.90 (0.84-0,96)	0.97 (0.90-1.04)	0.02
EULAR good response*	Ref.	0.82 (0.70-0.96)	0.95 (0.80-1.12)	0.84 (0.70-1.01)	0.96 (0.79-1.17)	0.10
DAS 28 remission*	Ref.	0.83 (0.70-0.98)	1.02 (0.85-1.21)	0.89 (0.74-1.08)	1.00 (0.82-1.23)	0.12
HAQ Improvement*	Ref.	0.82 (0.70-0.96)	1.04 (0.89-1.21)	0.86 (0.73-1.03)	0.86 (0.71-1.05)	0.02
28 joint counts = 0*	Ref.	0.74 (0.61-0.89)	0.91 (0.75-1.11)	0.85 (0.69-1.04)	0.91 (0.73-1.13)	0.03

*LUNDEX corrected (1).†Sex, age, disease duration, RF, co-treatment (methotrexate, glucocorticoids).

Certolizumab pegol: no placental/lactation transfer

Recent data from the CRIB and CRADLE studies show that there is hardly any to no placental/lactation transfer transfer of certolizumab pegol. The pharmacokinetic CRIB study assessed potential levels of placental transfer of certolizumab pegol in 16 women (≥ 30 weeks gestation) who were being treated with certolizumab pegol werden. Certolizumab pegol levels were assessed with a highly sensitive certolizumab pegol-specific electrochemiluminescence immunoassay (lower limit of quantification (LLOQ)=0.032 µg/mL which is 10 times lower than previously used assays for certolizumab pegol) [17] [18]. The results showed that certolizumab pegol levels in 13/14 blood samples of the infants at the time of birth were below LLOQ as well as in all samples taken at week 4 and 8. One infant had a minimal level of certolizumab pegol of 0.042 µg/mL (49.4 µg/mL in the mother, and the child/mother plasma ratio was 0.009). At no time point during the study certolizumab pegol antilibodies were observed. These findings indicate no exposure in utero during the 3rd trimester [19]. The CRADLE study assessed concentrations of certolizumab pegol in breast milk in 17 lactating women (≥ 6 weeks postpartum) who were being treated with certolizumab pegol. It also calculated the Average Daily Infant Dose (ADID) of maternal certolizumab pegol. At steady state (≥ 3 doses certolizumab pegol) samples breast milk were collected at day 0, 14 or 28. Again, the highly sensitive certolizumab pegol-specific electrochemiluminescence immunoassay was used. The estimated ADID ranged between 0-0.0104 mg/kg/day; the median relative infant dose (RID) calculated post-hoc was 0.15%. In general, the AEs of mothers were similar to what was already known with regard to the safety profile of certolizumab pegol. The researchers concluded that the highest concentration certolizumab pegol in breast milk (0.0758 µg/mL) was <1% of the expected plasma concentration of a therapeutic dose [18] [20].

The median certolizumab pegol RID of 0.15% is considered safe for breastfeeding (RID <10%) [21]. These findings support continuation of treatment with certolizumab pegol during lactation [22].

Tofacitinib: safety and efficacy in open-label, long-term extension studies over 8 years

Wollenhaupt et al. reported safety, tolerability as well as clinical efficacy of tofacitinib in long-term extension (LTE) studies with up to 105 months of observation. Pooled data from two open-label studies of patients with RA who had participated in phase 1/2/3 tofacitinib studies were used. Patients received tofacitinib 5 or 10 mg twice daily (BID) as monotherapy or with background DMARDs. A total of 4,967 patients were treated (mean duration 1,215 days) and the total tofacitinib exposure amounted to 16,711 patient-years. Just over three quarters of patients (77.4%) maintained their initial dose. In total, 47.7% discontinued the treatment; in 22.8% of cases, this was due to AEs and in 3.5%, insufficient clinical response was the cause. The most frequent AE classes were infections and infestations (68.9%) followed by musculoskeletal/connective tissue disorders (39.0%). The most common AEs were nasopharyngitis (18.7%), upper respiratory tract infection (17.2%), bronchitis (12.2%) and urinary tract infection (12.2%). Serious AEs (SAEs) occurred in 28.6% of patients and serious infection events (SIEs) in 8.8% of patients. Malignancies (excluding non-melanoma skin cancer [NMSC]) were reported in 3.0% of patients. IRs (patients with events per 100 patient-years) for SAEs were 9.5, for SIEs 2.6 and for malignancies 0.9. IRs for SIEs and malignancies through month 105 did not increase compared with reported data through month 96. No new safety risks were identified. Clinical responses were sustained from month 1 to month 90 as is shown in Table 5 [23].

Table 5 Clinical outcomes in LTE studies (up to 90 months) of tofacitinib in RA patients [23]

	Tofacitinib (5 and 10 mg BID) ± background DMARDs		
	BL	Month 1	Month 90
		N=4907	N=171
ACR20 response rates, %	-	73.0	83.0
ACR50 response rates, %	-	49.2	56.1
ACR70 response rates, %	-	28.9	32.7
	N=4782	N=4776	N=168
DAS28-4 (ESR), mean (SE)	6.29 (0.01)	3.75 (0.02)	3.38 (0.09)
	N=4924	N=4880	N=170
HAQ-DI, mean (SE)	1.42 (0.01)	0.82 (0.01)	0.76 (0.05)
		N=4802	N=169
CDAI, mean change from BL (SE)	-	-24.0 (0.20)	-28.5 (1.02)

ACR20/50/70%: 20%/50%/70% improvement in modified American College of Rheumatology response criteria; DAS-28: 28 Joint count Disease Activity Score; HAQ-DI: Health Assessment Questionnaire- Disability Index

New therapies

Filgotinib: long-term safety and efficacy

Filgotinib - an oral Janus kinase (JAK)1 selective inhibitor – has shown to possess a favorable safety and efficacy profile in two 24-week phase 2b studies as add-on to methotrexate (DARWIN 1) or as monotherapy (DARWIN 2) in patients with active RA. Alten et al. assessed the long term safety and efficacy of filgotinib 200 mg daily in patients from the DARWIN 3 phase 2 open-label extension study. Patients who completed DARWIN 1 or 2 and enrolled in DARWIN 3 received filgotinib 200 mg once daily or 100 mg twice daily, depending on prior treatment assignment. For safety, all data from the first intake of filgotinib in DARWIN 1/2/3 was analysed (up to 144 weeks). In total, 877 patients participated in DARWIN 1 or 2, of which 739 patients entered DARWIN 3. Of those, 75.6% completed week 60, and 9.3% discontinued treatment due to positive Quantiferon, 7.8% due to other AEs, 6.8% for other reasons and 0.3% due to insufficient response. The overall exposure to filgotinib was 1,314 patient-years. The safety outcomes included treatment-emergent AEs (TEAEs), SAEs, SIs, herpes zoster (HZ), malignancies (with the exception of NMSC), major adverse cardiac events (MACE) and fatalities (Table 6).

Based on an observed case analysis 84%, 65%, 44% and 51% of patients reached ACR20, ACR50, ACR70 and DAS28 (C-reactive protein [CRP]) remission at week 60 respectively. It was concluded that these findings show that the safety profile of filgotinib appears consistent with that of previously reported double-blind studies and the clinical response appears durable [24].

Rapamycin: efficiency and safety with low-dose IL-2 treatment compared with methotrexate

Li et al. evaluated whether rapamycin – the inhibitor of molecular target rapamycin (mTOR) – could be beneficial in RA patients, and compared its efficiency and safety to methotrexate. Out of 58 DMARDs-naïve RA patients, 38 were treated with rapamycin

Table 6 Safety outcomes [24]

Event	IR per 100 patient-years
TEAEs*	157.7
SAEs*	5.3
SIs*†	1.9
HZ	1.2
Malignancies (excl. NMSC)	0.5
MACE	0.1
Fatalities	0.2

*Similar rates compared to the core studies †Infections decreased on a percentage basis from 15% (109/739, W0–12) to 5% (25/549, W85–96)

(0.5 mg every 2 days, combined with interleukin (IL)-2 50 WIU per day for 5 days), and 20 received methotrexate (10 mg per week). At baseline, patients had a mean DAS28 of 3.34. At week 1, the mean DAS28 after rapamycin treatment (2.43) and methotrexate (2.25) was not significantly different (P=0.43); the same was true for erythrocyte sedimentation rate (ESR; 24.74, 21.76, P=0.66, respectively). Both the dose of glucocorticoids during hospitalization and the length of hospital stay was lower for the rapamycin treatment group than for the methotrexate group (720.8 vs 1202.3, P=0.042 and 14.5 vs 21.0, P<0.001, respectively). The administration of rapamycin resulted in an increase in the absolute counts of Treg cells from a median of 36.82 cell/ul at week 0 to 99.80 cell/ul at week 1 (P<0.001). The ratios of Th17/Treg cells showed a significant reduction from a median of 0.16 to 0.09 (P=0.047). At 12 weeks, 5 patients treated with rapamycin dropped out due to non-compliance. The mean DAS28 was not significantly different (2.36, 2.16, P=0.51) as was the case for the daily dose of glucocorticoids (10.21, 9.16, P=0.804). The absolute counts of Treg cells increased from a median of 36.82 cell/ul at baseline to 43.26 cell/ul after the administration of rapamycin (P=0.028). The ratios of Th17/Treg showed no significant difference, starting from a median of 0.16 at baseline to 0.12 at week 12 (P=0.937). Two patients had liver enzyme elevations after methotrexate therapy for 1 week. However, no SAEs were observed during the 12-week period of rapamycin treatment and it was concluded that rapamycin in combination with low-dose IL-2 appears to be a safe and effective RA therapy [25].

Biosimilars

New biosimilar for adalimumab treatment efficacy at 24 weeks is similar with adalimumab

A new biosimilar for adalimumab (FKB327) has been assessed in patients with moderate to severe RA. Eligible patients – recruited at 105 centres – had a disease duration of ≥3 months and were poorly controlled on methotrexate as were those with elevated CRP levels of 10 mg/L or greater. No previous adalimumab treatment was allowed, but a history of one TNF-inhibitor or biologic was permitted. Treatments were administered as 40 mg subcutaneous (SC) injections every other week while patients continued receiving methotrexate. A total of 366 patients were randomly assigned to receive FKB327; another 362 received the reference product. The study's primary endpoint for bioequivalent efficacy was met as ACR20 was achieved by 74.4% of the FKB327 patients and 75.7% of the adalimumab patients. DAS28-CRP at week 24 – a key secondary endpoint - was the same for both groups and the proportion of patients achieving the additional secondary endpoints of ACR20, ACR50, and ACR70 over time were totally comparable between the two treatment groups. The AE profile was similar for both the reference product and FBK327. Pharyngitis, respiratory infections, and urinary tract infections were the most common AEs. Discontinuations in both groups were very low. During the study, one death occurred due to disseminated tuberculosis (TB) which might have been treatment-related. Nevertheless, very low numbers of active TB overall were observed (one case in the FKB327 group and three in the adalimumab group, which might be attributed to the high prevalence of TB in some of the countries where the study was performed). Immunogenicity findings were comparable between the treatment groups, with approximately 60% of participants in each group being positive for antidrug antibodies. Further studies are currently looking into long-term data to obtain more insight into the effect of switching to the biosimilar [26].

References

1. Linauskas A, et al. Body fat percentage and waist circumference were associated with the development of Rheumatoid Arthritis – a Danish follow-up study. OP0079. EULAR 2017.
2. Seror R, et al. Passive smoking in childhood and history of chronic diarrhoea increases the risk of developing Rheumatoid Arthritis (RA). OP0253. EULAR 2017.
3. Van den Oever IAM, et al. Management of cardiovascular risk in patients with Rheumatoid Arthritis: evidence and expert opinion. Ther Adv Musculoskel Dis. 2013;5(4):166-181.
4. Agca R, et al. EULAR recommendations for cardiovascular disease risk management in patients with Rheumatoid Arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis. 2017;76:17-28.
5. Filhol E, et al. Decrease in cardiovascular event excess risk in Rheumatoid Arthritis since 2000: a meta-analysis of controlled studies. OP0146. EULAR 2017.
6. Smolen JS, et al. EULAR recommendations for the management of Rheumatoid Arthritis with synthetic and biological Disease-Modifying Anti-Rheumatic Drugs: 2013 update. Ann Rheum Dis. 2014;73:492-509.
7. Michelsen B, et al. Depression and anxiety reduce the likelihood of achieving remission in patients with Rheumatoid Arthritis: real life data from the NOR-DMARD STUDY. THU0080. EULAR 2017.
8. Schiff MH. Preventing the Progression from Undifferentiated Arthritis to Rheumatoid Arthritis: The Clinical and Economic Implications. Am J Manag Care. 2010;16:S243-S248.
9. Demoruelle MK, et al. Treatment Strategies in Early Rheumatoid Arthritis and Prevention of Rheumatoid Arthritis. Current Rheumatology reports. 2012;14(5):472-480.
10. Gerlag DM, et al. Towards prevention of autoantibody-positive Rheumatoid Arthritis: from lifestyle modification to preventive treatment. Rheumatology. 2016; 55(4):607-614.
11. Hugues B, et al. Does a very early therapeutic intervention in very early arthritis / pre-rheumatoid arthritis patients prevent the onset of Rheumatoid Arthritis: a systematic review and metanalysis. OP0011. EULAR 2017.
12. Cordtz R, et al. Incidence of knee and hip replacements in Rheumatoid Arthritis patients following introduction of biological DMARDs: an interrupted time series analysis using nationwide health care registers. OP0251. EULAR 2017.
13. Raaschou P, et al. TNF inhibitor treatment and risk of cancer recurrence in patients with Rheumatoid Arthritis: a nationwide cohort study from Sweden. OP0308. EULAR 2017.
14. Goh ET, et al. Factors associated with treatment adherence in Rheumatoid Arthritis: a systematic literature review. THU0073. EULAR 2017.
15. Caporali R, et al. Induction of remission and maintenance in early, aggressive

Rheumatoid Arthritis using adalimumab in combination with methotrexate with or without short-term highdose glucocorticoids: results of a phase IV multicenter, randomized, double blind study (clintrial.gov: NCT00480272). OP0015. EULAR 2017.
16. Turesson C, et al. Comparative effectiveness at 1 year of different anti-TNF drugs as first biologic DMARD in patients with Rheumatoid Arthritis - results from the nationwide Swedish register. OP0016. EULAR 2017.
17. Mahadevan U, et al. Placental transfer of Anti-Tumor Necrosis Factor agents in pregnant patients with Inflammatory Bowel Disease. Clin Gastroenterol Hepatol. 2013;11:286-92.
18. Lacroix BD. Dosing with certolizumab pegol (CZP) 200 mg every 2 weeks (Q2w) provides higher plasma trough concentrations than 400 mg every 4 weeks (Q4w). Gastroenterology. 2010;138:S163-4.
19. Mariette X, et al. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, multicenter, pharmacokinetic study. OP0017. EULAR 2017.
20. Smolen JS, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active Rheumatoid Arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. 2009;68(6):797-804.
21. Hale TW. Textbook of Human Lactation. Amarillo, Texas: Hale Publishing, 2007.
22. Clowse MEB, et al. Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicenter, pharmacokinetic study. FRI0179. EULAR 2017.
23. Wollenhaupt J, et al. Tofacitinib, an oral Janus Kinase inhibitor, in the treatment of Rheumatoid Arthritis: safety and efficacy in open-label, long-term extension studies over 8 years. THU0197. EULAR 2017.
24. Alten R, et al. Long-term safety and efficacy of filgotinib in a Phase 2b open label extension study in patients with Rheumatoid Arthritis: results up to 144 weeks. THU0173. EULAR 2017.
25. Li Z, et al. Efficiency and safety of rapamycin combined with low-dose IL-2 treatment compared with methotrexate in patients with Rheumatoid Arthritis. THU0176. EULAR 2017.
26. Alten R, et al. Efficacy and safety results of a Phase III study comparing FKB327, an adalimumab biosimilar, with the adalimumab reference product, in patients with Active Rheumatoid Arthritis. OP0021. EULAR 2017.

Spondyloarthritis

Lifestyle factors such as smoking and obesity can fiercely impact the development and progression of the disease as well as treatment response. The number of spondyloarthritis (SpA) treatments is still expanding, which also includes biosimilars.

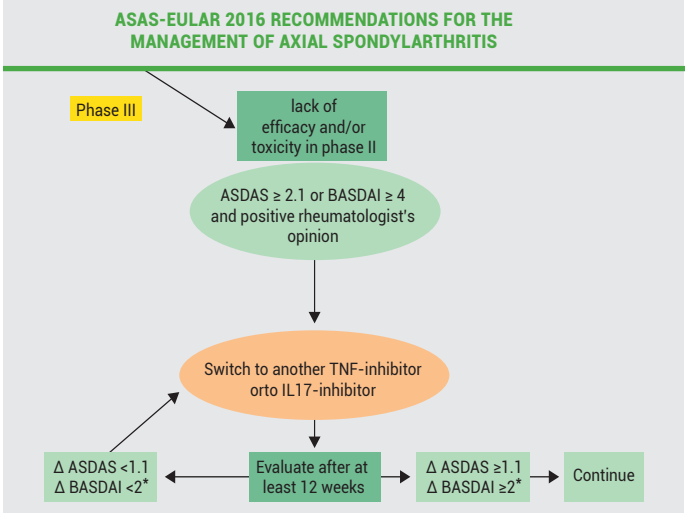
New treat-to-target recommendations

The question whether treat-to-target (T2T) is applicable in SpA was answered by Braun, who stated that while it is much easier to define remission in RA, remission as a target in SpA with axial involvement is a largely complex matter. The majority of published studies have demonstrated that overall mortality and morbidity in SpA is linked to disease activity. Existent treatment guidelines are helpful in achieving treatment. When used in an T2T approach, ASDAS showed to be an effective outcome measure in axSpA which is comparable to DAS as used in RA. Therefore, T2T can be effectively used in SpA which would benefit patients (Figure 2) [1].

TNF-inhibitors reduce radiographic progression in AS

Whether TNF-inhibitors have an influence on radiographic progression in ankylosing spondylitis (AS) remains controversial. Molnar et al. investigated the impact of TNF-inhibitor use on spinal radiographic progression in AS in 420 patients with AS. These patients contributed to data for 597 X-ray intervals in adjusted analyses (1–5 intervals per patient). The majority of patients (66%) was male, 81% had HLA-B27, and the mean age was 40.4 years. Mean disease duration was 13.9 years, mSASSS was 6.4, ASDAS 2.8 and 39% of the patients were already using TNF-inhibitors at the time of their first X-ray. Mean mSASSS progression in 2 years was 0.9 units. It was shown that prior use of TNF-inhibitors reduced the odds of progression in the next 2-year interval by 49% (OR 0.51, 95% CI 0.28-0.92, P=0.03). Baseline mSASSS and male sex also significantly affected progression. Adding ASDAS as a covariate to the model decreased the estimated effect of TNF-inhibitors on progression (OR 0.65, 95% CI 0.36-1.17, P=0.15). In this model, a decrease in ASDAS by 1 unit would lower the odds for progression by 0.62 (P=0.001; Table 7) [2]. It was concluded that TNF-inhibitors seem to reduce radiographic progression in patients with AS and this effect is mediated, at least in part, by a decrease in disease activity [2].

Figure 2 ASAS-EULAR 2016 recommendations for the management of axSpA [1]



ASDAS- Ankylosing Spondylitis Disease Activity Score; BASDAI- Bath Ankylosing Spondylitis Disease Activity Index *Either BASDAI or ASDAS, but the same outcome per patient.

Table 7 Longitudinal multivariable analysis of radiographic progression [2]

Variable	OR	95% CI	P value
TNF-inhibitor use prior to X-ray interval	0.51	0.28-0.92	0.03
NSAID use at start of X-ray interval	0.81	0.40-1.63	0.55
mSASSS at start X-ray interval	1.06	1.04-1.07	<0.001
Male gender	3.01	1.56-5.77	0.001
Disease duration	1.01	0.99-1.04	0.38
Current smoking	0.94	0.55-1.61	0.83
HLA-B27	0.99	0.46-2.12	0.98
Number of exercise sessions per week	0.93	0.80-1.08	0.35
Peripheral arthritis	1.00	0.56-1.79	1.00

The role of smoking in the development and progression of structural damage in AS

Evidence has been found in the past that smoking, among other risk factors, increases the risk of developing AS [3]. To determine whether smoking is associated with more rapid spinal damage and disease progression seen on X-rays in AS patients, a detailed review and meta-analysis of all the relevant and currently available studies was conducted by Akar et al. The combined data taken from 8 eligible studies suggested a significant association between smoking and cumulative spinal structural damage (odds ratio [OR] 2.02). Data from studies investigating the association between smoking and disease progression on spinal X-rays reflected in the formation of new bony growths (syndesmophytes) and/or an increase in size of syndesmophytes is still being assessed. According to the researchers, smoking constitutes a major risk factor, not only for disease susceptibility but also with regard to disease severity in AS patients. Needless to say, encouraging AS patients to stop smoking could have a major impact on their future quality of life (QoL) [4].

Impact of obesity on TNF-inhibitors

Obesity is associated with significantly lower response rates to TNF-inhibitors in patients with axSpA as was shown in a study by Micheroli et al. In 632 axSpA patients, the impact of different BMI categories on the response to TNF-inhibitors was assessed. Patients were categorized according to BMI: normal (BMI 18.5 to <25), overweight (BMI 25-30) and obese (BMI >30). Researchers evaluated the proportion of patients achieving Assessment in SpondyloArthritis international Society 40% (ASAS40) as well as Ankylosing Spondylitis Disease Activity Score (ASDAS) improvement and status scores at 1 year. Patients who had discontinued the TNF-inhibitors were considered to be non-responders. Results were controlled for age, sex, human leukocyte antigen (HLA)-B27, axSpA-type, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Metrology Index (BASMI), elevated CRP, current smoking and physical exercise in multiple adjusted logistic regression analyses. Compared to patients who were a normal weight/ overweight, the obese individuals were significantly older, had a longer symptom duration and higher Bath Ankylosing Spondylitis Functional Index (BASFI) and BASMI levels. However, ASDAS levels were comparable between the 3 groups. ASAS40 response was reached by 44%, 35% and 28% of patients with normal weight, overweight and obesity, respectively, (P=0.02; data available of 78% of patients). A significantly lower OR for achieving ASAS40 response was found in adjusted analyses in obese patients vs patients with normal BMI (OR 0.30). Comparable results were found for the other outcomes assessed. The respective adjusted ASAS40 OR in overweight vs normal weight patients was 0.69 [5].

Treatment

Golimumab: results through week 28

The GO-ALIVE study – a phase 3, multicenter, randomized, double-blind, placebo-controlled trial – was designed to evaluate the safety and efficacy of intravenous (IV) golimumab in 208 adult patients with active AS. They were randomized 1:1 to IV golimumab 2 mg/kg at weeks 0, 4, and every 8 weeks (N=105) or placebo (N=103) at weeks 0, 4, and 12, with crossover to golimumab at week 16. Up to 20% of patients could have had a prior anti-TNF agent (other than golimumab), and up to 10% of patients could have complete ankylosis of the spine. The primary endpoint of the study was ASAS20 at week 16. Major secondary endpoints were ASAS40, BASDAI50, and change in BASFI score at week 16. Data through week 28 show that at week 16, significantly greater proportions of golimumab patients had ASAS20 compared to placebo patients (73.3% vs 26.2%). The same was the case for ASAS40 (47.6% vs 8.7%), and BASDAI50 (41.0% vs 14.6%) responses (all P<0.001). Reductions in BASFI were also significantly greater with golimumab. With regard to the timing of the ASAS20 response, golimumab patients experienced this early as week 2, which was significantly higher than placebo (37.1% vs 19.4%; P=0.005). Responses in the golimumab group were maintained through week 28. Those placebo patients crossing over to golimumab at week 16 had improvements in clinical response at week 20 which were maintained through week 28. Through week 16, 23.3% of placebo patients and 32.4% of golimumab patients experienced ≥1 AE. The most common type of AE were infections (placebo 7.8%; golimumab 11.4%). Through week

28, 34.8% of all golimumab-treated patients had ≥1 AE of which nasopharyngitis (5.4%) was the most common. SAEs occurred in 1.0% of patients (pancreatitis, N=1; pneumonia, N=1), both of whom were randomized to golimumab. There were no opportunistic infections, malignancies, or deaths through week 28. With 1.5%, the rate of infusion reactions was low with 3 golimumab patients experiencing 4 reactions, none of which was serious or severe [6].

Secukinumab; long term efficacy and safety

Secukinumab – a fully human anti-IL-17A monoclonal antibody – has been assessed in the Phase 3 MEASURE studies. Baraliakos et al. reported efficacy and safety of secukinumab through 3 years in an extension trial to the core MEASURE 1 trial. Patients who were treated with secukinumab 150 or 75mg SC were invited to enter a 3-year extension trial. Of the 371 patients who were enrolled in the 2-year core trial, 78% completed this trial. Of these, 274 patients entered the extension trial, of which 95% completed 156 weeks of treatment.

At week 156, clinical improvements were sustained across all endpoints and similar trends were observed regardless of prior anti-TNF use (Table 8). The total exposure to secukinumab over the entire treatment period was 950.4 patient-years. Two deaths occurred in the study period and no deaths occurred during the first year of the extension study. Pooled data (N=360) for secukinumab 75 and 150 mg show that 86.7% had any AE; for SAEs this was 16.7%. The most frequent AEs were nasopharyngitis (24.7%), diarrhoea (14.2%), headache (14.2%), upper respiratory tract infection (13.1%), influenza (11.1%) and pharyngitis (9.7%).

Table 8 Summary of the efficacy results at week 156 for secukinumab [7]

	Observed data		Missing data considered[a]	
	Secukinumab IV --> 150 mg (N=87)	Secukinumab IV --> 75 mg (N=100)	Secukinumab IV --> 150 mg (N=87)	Secukinumab IV --> 75 mg (N=100)
ASAS, % resonse				
ASA S20/40	80/62[b]	76/50[b]	80/61	75/50
ASAS PR	27[b]	14[b]	27	14
BASDAI				
Baseline, mean±SD	6.1±1.5	6.0±1.5	6.1±1.5[#]	6.0±1.5[#]
Mean change from baseline[c]	-3.3+2.4[b]	-3.0±1.7[b]	-3.1±0.2	-2.9±0.2
	Secukinumab IV --> 150 mg		Secukinumab IV --> 75 mg	
Analysis by anti-TNF status[d]				
Anti-TNF-naïve[e]	N=70		N=76	
ASA S20/40, % response	80/61		76/48	
Anti-TNF-IR[e]	N=17		N=24	
ASA S20/40, % response	81/63		74/57	

a-Missing data of binary variables were imputed and for continuous variables MMRM estimates are shown. b- Evaluable data available in N=86 and N=98 pts in the secukinumab IV-->150mg and IV-->75mg groups, respectively. c- Least squares mean±SE for MMRM estimates and mean ±SD for observed data. d- Observed data. e- Evaluable data available in N=70 and 75 pts (naïve) and N=16 and 23 pts (IR) in the secukinumab IV-->150mg and IV-->75mg groups, respectively. # -Observed data provided for reference. IV, pts received secukinumab 10mg/kg i.v. loading at baseline, Wks 2 and 4. n- number of pts in the extension trial.

In summary, secukinumab provided sustained efficacy in signs/symptoms and physical function in patients with active AS over 3 years with a favourable and well tolerated safety profile [7].

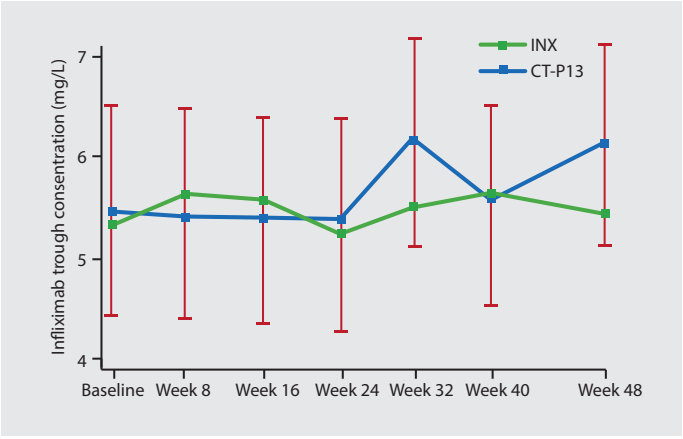
Adalimumab: tapering with combined methotrexate can be effective as maintenance therapy in SpA-related uveitis

A Chinese study by Lian et al. investigated the effectiveness and safety of an adalimumab tapering strategy in SpA-related uveitis when combined with methotrexate. This was done by a retrospective analysis. In 32 patients with SpA-related uveitis who achieved clinical remission for at least 6 months after receiving a standard dose of adalimumab in combination of methotrexate, adalimumab was tapered and methotrexate was continued. The dosing intervals of adalimumab were spaced by 30% every 3 months up to a complete stop. A total of 26 cases without methotrexate were analyzed to compare with the tapered group. No significant differences in demographic characteristics, BASDAI, CRP, and ESR were observed between the two groups at baseline. During the first 12 months of adalimumab tapering, the mean BASDAI remained stable in both groups. No recurrent uveitis was found in the group with combined methotrexate whereas in the group without combined methotrexate, 7.7% of patients had increased anterior chamber inflammation and visual acuity. At the end of 24 months, mean BASDAI, CRP and ESR remained low in both groups. A total of 6.3% of patients in the group of combined methotrexate had increased BASDAI >4, but no recurrent uveitis was observed. Altogether, 15.6% of patients in the group of combined methotrexate had recurrent uveitis, of which 80% initiated adalimumab tapering at 6 months' remission. In comparison, 30.8% of patients in the group without combined methotrexate had recurrent uveitis, of which 6 cases initiated adalimumab tapering at 6 months' remission and 2 cases initiated adalimumab tapering at 9-12 months' remission. Recurrent uveitis at 12 months' remission or longer was not seen in any patient in both groups. Adalimumab plus methotrexate were well tolerated by all patients. It was concluded that to maintain remission of SpA-related uveitis, adalimumab tapering can be effective when combined with methotrexate. Initiation of the tapering after 12 months' remission largely lowers the rate of recurrence [8].

Use of biosimilars in SpA

In the NOR-SWITCH study, patients with Crohn's disease (CD), ulcerative colitis (UC), SpA, RA, psoriatic arthritis (PsA)

Figure 3 Serum levels originator infliximab and CT-P13 [9]



and plaque psoriasis (Ps) on stable treatment with originator infliximab (N=45), were compared with patients who switched to CT-P13 (biosimilar infliximab, N=46). This was a 52-week randomized, double-blind, non-inferiority, Phase 4 trial which investigated efficacy, safety and immunogenicity. The primary endpoint was disease worsening according to disease-specific composite measures and/or consensus between investigator/patient. The results showed that demographics, occurrence of disease worsening, change in disease measures and TEAEs were similar between the two patient groups. The same was true for the serum drug levels for originator infliximab and CT-P13 (Figure 3).

In summary, these explorative analyses showed similar efficacy, drug levels and safety in SpA patients who switched to CT-P13 as those on continuous originator infliximab. However, it should be noted that the study was not powered to show non-inferiority within each diagnosis [9].

References

1. Braun J. The concept of treat-to-target. SP0054. EULAR 2017.
2. Molnar C, et al. Tumor Necrosis Factor Inhibitor treatment reduces spinal radiographic progression in Ankylosing Spondylitis by decreasing disease activity: a longitudinal analysis in a large prospective cohort. OP0189. EULAR 2017.
3. Videm V, et al. Current Smoking is Associated with Incident Ankylosing Spondylitis - The HUNT Population-based Norwegian Health Study. The Journal of Rheumatology. 2014;41(10):2041-2048.
4. Akar S, et al. The role of smoking in the development and progression of structural damage in patients with Ankylosing Spondylitis: the preliminary results of a systematic review and meta-analysis. OP0120. EULAR 2017.
5. Micherolo R, et al. Impact of obesity on the response to Tumour Necrosis Factor Inhibitors in Axial Spondyloarthritis. THU0347. EULAR 2017.
6. Deodhar A, et al. Safety and efficacy of intravenous golimumab in adult patients with active ankylosing spondylitis: results through week 28. THU0348. EULAR 2017.
7. Baraliakos X, et al. Secukinumab provides sustained improvements in the signs and symptoms of Active Ankylosing Spondylitis: 3-year results from a Phase 3 Extension Trial (MEASURE 1). THU0397. EULAR 2017.
8. Lian F, et al. Adalimumab tapering with combined methotrexate can be effective as maintenance therapy in spa-related uveitis.THU0351. EULAR 2017.
9. Goll GL, et al. Disease worsening and safety in patients switching from originator infliximab to biosimilar infliximab (CT-P13) in the randomized NOR-SWITCH-study: explorative analysis in SPA patients. THU0354. EULAR 2017.

Psoriatic Arthritis

The complexity of PsA can be challenging, for physicians as well as for patients. The increasing use of patient-reported outcomes (PROs) could aid understanding as well as provide insights into patient's experiences and the effects of the condition on their lives. Ongoing research into new treatment modalities and new drugs may contribute to obtaining better control of the disease.

PROs: impact of PsA

PROs are becoming increasingly important in measuring the effect of (medical) intervention and/or treatment throughout all fields of medicine. A non-interventional, cross-sectional, descriptive, exploratory analysis aimed to characterise patients with PsA in the 2016 National Health and Wellness Survey (NHWS) and determine the impact of treatment, or no treatment, on PROs. The NHWS was a self-administered web-based questionnaire which contained a sample of adults in France, Germany, Italy, Spain and the United Kingdom (UK). Respondents completing the arthritis module and reporting PsA diagnosis were stratified by advanced therapies (TNF-inhibitors, IL-antagonists, phosphodiesterase-4 [PDE4] inhibitors) ± other drugs; other therapies (such as conventional synthetic DMARDs, glucocorticoids, topical medications), or no current treatment. The NHWS was completed by 80,600 adults; 947 completed the arthritis module and self-reported PsA diagnosis. Of these, 7% reported receiving advanced therapies, 29% had other therapies and 64%had no current treatment. Age and gender were generally balanced between the groups, though more patients on advanced therapies had a BMI ≥30 (41%) vs other therapies (34%) and no current treatment (26%). Patients who had advanced therapies reported more comorbidities vs patients on other therapies and patients with no current treatment (mean 2.2 vs mean 1.8 and mean 1.7)

Table 9 Mean outcome scores by treatment type [1]

	Advanced therapies N=65	Other therapies N=274	Not treated N=608
SF-36 MCS SF- 36 PCS	38.0 (11.0) 36.0 (9.9)	40.1 (11.6) 37.6 (9.6)	39.8 (10.5) 43.9 (8.4)
PHQ-9 total scores[a]	7.7 (7.0)	9.1 (6.8)	7.8 (7.1)
WPAI domain scores[b] % work missed % impairment at work % overall work impairment % activity impairment	 26.8 (29.7) 55.8 (31.1) 61.4 (34.2) 62.0 (26.1)	 27.8 (35.4) 42.8 (29.6) 49.0 (33.2) 57.8 (26.5)	 20.8 (27.8) 44.5 (29.3) 51.1 (32.6) 48.3 (28.9)

a N=22, 45, 137 for advance therapies, other therapies, not treated, respectively. b N for WPAI % work missed = 33, 113, 338, respectively for advanced therapies, other therapies, not treated, N for WPAI% impairment at work and overall work impairment=33, 99, 328 respectively, for advanced therapies, other therapies, not treated; MCS: Mental Component Summary; PCS: Physical Component Summary; PHQ-9: Patient Health Questionnaire-9; SD: Standard Deviation; SF-36: Short form-36 Health Survey; WPAI: Work Productivity and Activity Impairment Questionnaire.

More patients on advanced therapies were current smokers (49%) vs those on other therapies (30%) and those with no current treatment (32%). Prior to treatment with advanced or other therapies, 94% and 82% self-reported moderate or severe PsA, falling to 58% and 59%, respectively, after treatment, compared with 36% of patients with no current treatment. SF-36 scores and Patient Health Questionnaire-9 (PHQ-9) scores did not widely vary across groups. Regardless of treatment groups, patients reported >20% work loss, >45% overall work impairment and >45% activity impairment (Table 9).

Table 10 Efficacy outcomes at week 24 in mITT[a] population [2]

Efficacy Endpoints	PBO	GUS	P-value
ACR 20	18.4%	58.0%	P<0.001
ACR 50	10.2%	34.0%	P=0.002
ACR 70	2.0%	14.0%	P=0.023 (P H)
PASI 75	12.5%	78.6%	P<0.001
PASI 90	6.3%	66.3%	P<0.001
PASI 100	6.3%	39.8%	P<0.001
Mean (SD) change from BL in HAQ-DI score	-0.006 (0.53)	-0.42 (0.51)	P<0.001
Median % change from BL in Lei[b]	-33.33%	-100.00%	P=0.009
% of pts with unresolved enthsitis[b]	71.0%	43.4%	P=0.012
Median % change from BL in dactylitis[c]	-33.33%	-100.00%	P<0.001
% of pts with unresolved dactylitis[c]	82.6%	44.8%	P=0.001
Mean (SD) change from BL in SF-36 PCS score	0.46 (6.51)	6.59 (7.47)	P<0.001
Mean (SD) change from BL in SF-36 MCS score	0.42 (6.74)	4.95 (9.06)	P=0.002
% of pts achieving Minimal Disease Activity	2.0%	23.0%	P=0.001
Mean (SD) change from BL in PASDAS	-0.49 (1.33)	-2.50 (1.59)	P<0.001
Mean (SD) change from BL in Grace Index	-0.35 (1.39)	-2.73 (1.76)	P<0.001
Mean (SD) change from BL in mCPDAI	-0.8 (2.26)	-3.9 (2.79)	P<0.001
Mean (SD) change from BL in DAPSA	-4.97 (20.11)	-23.08 (20.21)	P<0.001

a All pts randomized into study, received at least 1 administration of study treatment (GUS or PBO), and were analysed according to their assigned treatment group regardless of their actual treatment received; b Among the pts with enthesitis at baseline (PBO: N=31; GUS: N= 76); c Among the patients with dactylitis at baseline (PBO: N=23; GUS: N= 58); Lei: Leeds Enthesitis Index, PCS: Physical Component Score, MCS: Mental Component Score; PASDAS: Psoriatic Arthritis Disease Activity Score; GRACE: GRAppa Composite Score; mCPDAI: Modified Composite Psoriatic Disease Activity Index; DAPSA : Disease Activity Index for Psoriatic Arthritis; BL: Baseline

These findings bring some important issues to light, such as that the fact that >60% of patients reporting their PsA diagnosis reported no current treatment. Also, as >50% of treated patients reported moderate or severe PsA, this suggests a clear need for overall better management of PsA to reduce the disease impact and improve the QoL. However, the results need to be interpreted with caution, as the researchers pointed out that they are limited by the self-reported PsA diagnosis, which may differ from physician-reported PsA diagnosis. Also, the survey was conducted in the European Union (EU) only, which may differ from other parts of the world. Furthermore, further statistical analyses are needed to determine differences between groups and correlation to other health indicators [1].

Guselkumab: efficacy and safety through week 24

Guselkumab – a fully human monoclonal antibody targeting IL-23 – demonstrated significant improvement in joint symptoms, physical function, psoriasis, enthesitis, dactylitis and QoL in 149 patients with active PsA and 3% or more of their body surface area affected by plaque psoriasis despite current or previous treatment with standard-of-care therapies (including anti-TNF treatment). Patients received either 100 mg SC guselkumab, or placebo at baseline and week 4 followed by every 8 weeks through week 44. Patients in both arms who had <5% improvement from baseline in swollen and tender joint counts by week 16 were able to qualify for an early escape and switch to open-label therapy with ustekinumab. All remaining placebo patients crossed over to the guselkumab arm at week 24. The results demonstrated that as early as 4 weeks into treatment, 21% of patients in the guselkumab group showed a significant treatment effect in ACR20 response, versus none in the placebo group (P<0.001). The ACR response in the active arm increased with time: 58% of subjects reached a 20% improvement in joint symptoms at week 24, versus 18.4% of those in the placebo group (P<0.001). ACR70 was achieved by 14% of patients on guselkumab versus 2% on placebo at week 24 (P=0.023). Resolved enthesitis occurred in 29.0% of those patients with enthesitis at baseline in the placebo group at week 24, versus 56.6% on guselkumab (P=0.012). Resolution from baseline to week 24 for dactylitis (in those patients with dactylitis at baseline) was 17.4% of patients on placebo, versus 55.2% on guselkumab (P<0.001). The percentage of patients achieving minimal disease activity at week 24 was 2% for placebo compared to 23% in the guselkumab group (P=0.001). Patients in the active arm also seemed to experience mental benefits, with significantly higher scores

on the SF-36 mental component summary (P=0.002), in addition to significantly higher physical component scores (P<0.001; Table 10).

Furthermore, guselkumab was well tolerated as the proportion of patients with at least 1 AE was comparable between both groups (guselkumab 36.0% vs placebo 32.7%) through week 24. The most common AEs were infections (guselkumab 17.0% vs placebo 20.4%); no serious infections, cases of cancer or death during the 24 weeks of the study were reported. Currently, guselkumab is evaluated in a Phase 3 development program for PsA and might be a promising new treatment for PsA [2].

Apremilast: associated with long-term DAS28 remission

Edwards et al. reported the impact of apremilast on PsA manifestations over 4 years. A total of 505 patients were stratified by baseline DMARD use (yes/no) and psoriasis involvement of the body surface area (<3%/≥3%) and randomized (1:1:1) to placebo (N=169), apremilast 30 mg twice daily (N=167), or apremilast 20 mg twice daily (N=169). After the 24-week placebo-controlled phase, all patients were treated with apremilast 30 mg or apremilast 20 mg and could enroll in the LTE. Efficacy assessments were conducted through week 208. Of the total number of patients, 91% who started the 4th year of apremilast therapy completed the visit at week 208. Patients treated with apremilast 30 mg demonstrated sustained decreases in disease activity at week 208, as was shown by mean change from baseline in DAS28 (CRP) of -1.66; 80.3% achieved good/moderate EULAR response and 50.4% achieved DAS28 (CRP) remission. Sustained effect on inflammation at week 208 was also demonstrated by mean/median percent changes in swollen joint count (SJC) of −77.4%/−100.0%; 64.8% of patients had an SJC of 0 or 1. Decreases in disability and maintenance of functionality were shown by sustained improvements in Health Assessment Questionnaire-Disability Index (HAQ-DI) scores. A continued effect on skin disease was shown by decreases in skin involvement, as measured by the Psoriasis Area and Severity Index (PASI). A total of 54.7% of apremilast 30 mg patients had baseline PASI >5 and 27.3% had baseline PASI >10; at week 208, 64.5% had PASI <3 and 77.4% had PASI ≤5. PASI-75 and PASI-50 response rates also demonstrated clinically significant relief (Table 11). In patients treated with apremilast 20 mg, similar findings were observed at week 208. Through 208 weeks of apremilast 30 mg therapy, no new safety concerns were identified.

Table 11 Outcomes at week 208 [3]

	APR30 N=129*
DAS-28 (CPR), mean change	-166
DAS-28 (CPR),<2.6 n/m (%)	64/127 (50.4)
SJC, mean/median % change	-77.4/-100.0
TJC, mean/median % change	-64.4/-86.6
HAQ-DI (0-3), mean change	-0.42
HAQ-DI MCID ≥0.30/≥0.35, n/m (%)	63/129 (48.8)
ACR20, n/m (%)	85/128 (66.4)
ACR50, n/m (%)	51/128 (39.8)
ACR70, n/m (%)	31/127 (24.4)
PASI-75, n/m (%)$	28/62 (45.2)
PASI-50, n/m (%) $	42/62 (67.7)

*The n reflects the number of patients treated with APR30, regardless of when APR was started(BL, Weeks 16, or Week 24) and who had data available at Week 208; actual number of patients available for each endpoint may vary. $ Examined among patients with psoriasis involvement of the body surface area ≥ 3% at BL.APR 30: Aprimilast 30mg BID; DAS-28: 28 Joint count Disease Activity Score; CRP. C-reactive Protein; SJC: Swollen Joint Count; TJC: Tender Joint Count; HAQ-DI: Health Assessment Questionnaire- Disability Index ; MCID: Minimal Clinically Important Difference; ACR20/50/70%: 20%/50%/70% improvement in modified American College of Rheumatology response criteria; n/m: number of response/ number of patients with sufficient data for evaluation; PASI-75/50: ≥75%/50% reduction from BL Psoriatic Area and Severity Index Score;

During weeks >156 to ≤208 of apremilast 30 mg exposure, the only AE occurring in ≥5% of patients was nasopharyngitis; most AEs were mild or moderate in severity. SAEs occurred in 7.2% of apremilast 30 mg patients over weeks >156 to ≤208, which is similar to rates observed in earlier study periods. Only 0.7% discontinued due to AEs over weeks >156 to ≤208. The apremilast 20 mg and 30 mg safety profile was similar. It was concluded that over 208 weeks, apremilast demonstrated sustained and clinically important improvements in PsA signs and symptoms, including physical function and associated psoriasis, among patients continuing the study [3].

Secukinumab: results from the FUTURE 2 study

A post-hoc analysis of the FUTURE study evaluated change in pain scores from baseline to week 104 in PsA patients receiving secukinumab. The results reported are for secukinumab 300 and 150 mg in the overall population and stratified by prior use of TNF-inhibitor. The findings demonstrated that mean changes from baseline in pain visual analogue scale (VAS) were greater with secukinumab vs placebo by week 3 (least squares mean [LSM]: -16.9, -12.6 with secukinumab 300 and 150 mg, respectively vs -5.75 with placebo; P<0.05), and week 16 (LSM: -24.0 and -23.0 for secukinumab 300 and 150 mg, respectively vs -8.41 with placebo; P<0.05). Mean changes were sustained through week 104 (-26.1 and -25.9 with secukinumab 300 and 150 mg, respectively). In both secukinumab groups,

>50% patients reported improvements of ≥20% by week 3 and this increased through week 104. Similarly, SF-36 bodily pain domain scores improved from baseline by week 4 and 16 with secukinumab vs placebo, exceeding minimum clinically important differences of 5.0 (week 4: LSM: 16.2 and 16.3 for secukinumab 300 and 150 mg, respectively vs 5.9 with placebo; P<0.05 and week 16: LSM: 21.1 and 22.0 for secukinumab 300 and 150 mg, respectively vs 6.9 with placebo; P<0.05). Improvements in pain were consistent in TNF-inhibitor-naïve and TNF-inhibitor inadequate responder/intolerant patients and of greater magnitude in the naïve subgroup. Based on the EQ-5D-3L pain/discomfort item, 99% patients reported moderate to extreme pain or discomfort at baseline. At week 4, more patients in the secukinumab groups experienced no pain or discomfort 300 mg than in the placebo group (300 mg 15% and 150 mg 10% vs placebo 5%) and increased through week 104 to 28% and 16% with secukinumab 300 and 150 mg, respectively. The researchers stated that secukinumab provides rapid and sustained pain relief through 104 weeks in patients with PsA as assessed by multiple clinically relevant patient-reported measures of pain. Improvements were reported by patients regardless of their prior TNF-inhibitor therapy status [4].

Certolizumab pegol: results from RAPID-PsA study

The RAPID-PsA study evaluated if initial improvements in PROs during treatment with certolizumab pegol for 4 years were maintained. A total of 273 adult patients with active PsA who had failed on ≥1 DMARD were included. Patients who were originally randomised to certolizumab pegol (400 mg at week 0,2, and 4 [loading dose] followed by either 200 mg Q2W or 400 mg Q4W, continued their dose during the open-label period. Assessed PROs included Patient's Global Assessment of Arthritis Pain (PtAAP; VAS), fatigue (numeric rating scale), HAQ-DI, SF-36 Physical en Mental Component Summary (SF-36 PCS/MCS), Psoriatic Arthritis Quality of Life (PsAQoL) and Dermatology Life Quality Index (DLQI). Of the patients who were randomised to certolizumab pegol at week 0, 91% completed week 24 and 67% completed week 216. Improvements observed to week 24 of treatment were generally maintained for 4 years (until week 216) in all assessed PROs. Similar maintained improvements were observed in patients with and without prior anti-TNF exposure [5].

Tofacitinib: comparing safety with real-world data

Patients with active PsA who had not previously been prescribed an anti-TNF treatment and who were treated with tofacitinib – an oral Janus kinase inhibitor – had superior ACR20 response rates compared to placebo as well as in change from baseline in the HAQ-DI score at 3 months. Tofacitinib's superiority to placebo was shown as early as week 2, and was maintained for 12 months. Mease et al. randomised 422 patients 2:2:2: 1:1 to tofacitinib 5 or 10 mg twice daily, adalimumab 40 mg sc injection every 2 weeks, or placebo (advancing to tofacitinib 5 or 10 mg twice daily at 3 months). Patients were required to have stable treatment with 1 csDMARD. A total of 96.2% and 88.4% of patients completed 3 and 12 months treatment, respectively. At month 3, tofacitinib 5 and 10 mg twice daily showed a statistically significant improvement compared to placebo as measured by the ACR20 response (P≤0.05 and P<0.0001 respectively), and change from baseline in the HAQ-DI score (P≤0.05 and P<0.001). More than 91% of patients were radiographic non-progressors at 12 months. Safety findings were similar between the treatment groups at 12 months: the most common AEs were upper respiratory tract infection (7.5-10.6%), nasopharyngitis (7.5-11.5%) and headache

Table 12 Safety outcomes [6]

	Up to M3	Up to M12				
	Placebo (N=105)	Placebo --> tofacitinib 5 mg BID (N=52)	Placebo --> tofacitinib 10 mg BID (N=53)	Tofacitinib 5 mg BID (N=107)	Tofacitinib 10mg BID (N=104)	Adalimumnab 40 mg SC Q2W (N=106)
AEs, n (%)	37 (35.2)	36 (69.2)	34 (64.2)	71 (66.4)	74 (71.2)	76 (71.7)
SAEs, n (%)	1 (1,0)	3 (5.8)	4 (7.5)	8 (7.5)	4 (3.8)	9 (8.5)
Discontinuation due to AEs, n (%)	1 (1.0)	2 (3.8)	2 (3.8)	6 (5.6)	3 (2.9)	4 (3.8)
Deaths, n (%)	0	1(1.19)b	0	0	0	0
AEs of special interest, n (%) [day of onset]						
Serious infection	0	2 (3.8) [102, 331]	0	0	1 (1.0) [132]	1 (0.9) [170]
Herpes zoster	0	0	0	2 (1.9) [61, 173]	2 (1.9) [221, 317]	0
Malignancy	0	0	0	3 (2.8) [1, 11, 232]	1 (1.0) [103]	0
MACE	0	1 (1.9) [139]	0	0	0	2 (1.9) [263,345]

b Cardiac arrest; AE: Adverse Events; BID: Twice Daily; MACE: Major Adverse Cardiovascular EventS; n: number of patients; SAE: Serious Adverse Events; Q2W: Once every 2 Weeks; SC: Subcutaneous

(3.8-10.6%). There were no new safety risks identified compared to previous studies in other indications (Table 12) [6]. With regard to safety, Curtis et al. assessed the IRs for AEs of special interest in a tofacitinib cohort from the Phase 3 PsA trials with real-world experience in a comparison cohort from the US Truven MarketScan database. The tofacitinib cohort included adult patients from 2 Phase 3 studies; patients were grouped by those who received tofacitinib 5 (N=238) or 10 mg (N=236) twice daily in the 2 Phase 3 studies, and all patients who received ≥1 dose of tofacitinib in the 2 Phase 3 studies or the LTE (tofacitinib all doses, N=783). It was found that IRs for SIEs were lower for the tofacitinib cohort vs the comparison cohort; the tofacitinib cohort had a higher rate of HZ vs the comparison cohort. IRs for malignancies and MACE were similar between cohorts. Thus, IRs of AEs of special interest reported in tofacitinib PsA phase 3 studies were generally comparable to those in a general PsA population comprising patients receiving a range of biologic agents, except HZ, which was higher for patients treated with tofacitinib but similar to the incidence observed with tofacitinib treatment in other indications [7].

Ixekizumab: reduces disease activity after inadequate response to TNF-inhibitor

Ixekizumab – a monoclonal high affinity antibody which selectively targets IL-17A – has already shown to improve disease activity and physical function in bDMARD-naïve patients with active PsA [8]. Currently, the results from the phase 3 trial SPIRIT-P2 have become available. In this study, ixekizumab was evaluated in 363 adult patients with active PsA and a previous inadequate response to TNF-inhibitor. They were randomized 1:1:1 to SC administration of 80 mg ixekizumab either every 4 weeks (N=122) or every 2 weeks (N=123) following a 160 mg starting dose at week 0 or placebo (N=118). It was shown that at week 12 and week 24, significantly more patients who received ixekizumab every 4 weeks or ixekizumab every 2 weeks achieved Psoriasis Area and Severity Index (MDA), Pysician Global Assessment of psoriasis (mMDA), and Psoriatic Arthritis Response Criteria (PsARC) compared with patients receiving placebo. Results for MDA were similar to mMDA results within each treatment group at each time point. Also, the CPDAI total scores for patients receiving 4 weeks or 2 weeks ixekizumab were significantly improved compared with those of patients receiving placebo [9].

References

1. Gottlieb B, et al. Impact of Psoriatic Arthritis on Patient-Reported Outcomes in 5 European Union countries. FRI0484. EULAR 2017.
2. Deodhar A, et al. Efficacy and safety results of guselkumab, an anti-IL23 monoclonal antibody, in patients with active Psoriatic Arthritis over 24 weeks: a Phase 2A, randomized, double-blind, placebo-controlled study. OP0218. EULAR 2017.
3. Edwards CJ, et al. Apremilast is associated with long-term (4-year) DAS-28 (CRP) remission and improvements in skin disease: results from a phase III study in DMARD/biologic-experienced patients with Active Psoriatic Arthritis. FRI0487. EULAR 2017.
4. McInnes IB, et al. Secukinumab provides rapid and sustained pain relief in Psoriatic Arthritis: 2-year results from the FUTURE 2 study. FRI0494. EULAR 2017.
5. Gladman D, et al. Certolizumab pegol is associated with long-term improvements in Patient-Reported Outcomes in Psoriatic Arthritis: 4-year outcomes from the RAPID-PSA study. FRI0489. EULAR 2017.
6. Mease PJ, et al. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, or adalimumab in patients with active Psoriatic Arthritis and an inadequate response to conventional synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs): a randomised, placebo-controlled, Phase 3 trial. OP0216. EULAR 2017.
7. Curtis R, et al. Comparing tofacitinib safety profile in patients with Psoriatic Arthritis in clinical studies with real-world data. FRI0496. EULAR 2017.
8. Mease PJ, et al. Ann Rheum Dis. 2016;0:1-9.
9. Coates LC, et al. Ixekizumab reduces disease activity in active Psoriatic Arthritis Patients who had previous inadequate response to Tumour Necrosis Factor-Inhibitors. FRI0502. EULAR 2017.

Sjögren's Syndrome

The recently identified significant association between nontuberculous mycobacteria infection and newly diagnosed Sjögren's syndrome might have implications with regard to screening. It could be argued that screening for Sjögren's syndrome in any patient previously infected with nontuberculous mycobacteria might enable prompt diagnosis and treatment.

Increased risk Sjögren's syndrome with previous bacterial infection

A study by Chen et al. showed a link between newly-diagnosed Sjögren's syndrome and previous infection with nontuberculous mycobacteria. A total of 5,751 newly diagnosed cases were compared to 86,265 non-Sjögren's syndrome patients matched for age, sex, and year of first

diagnosis. The patients who were newly diagnosed were around 11 times more likely to have had a prior infection with nontuberculous mycobacteria than a matched group of controls (OR 11.24; 95% CI 2.37-53.24); the magnitude of the association between nontuberculous mycobacteria and Sjögren's syndrome risk was greatest among those patients aged between 45 and 65 years. TB infection itself did not appear to be associated with an increased risk of developing Sjögren's syndrome but the risk of TB is increased in patients with Sjögren's syndrome (Table 13).

Table 13 Univariate and multivariate analysis of bacterial infection and Sjögren's syndrome [1]

	Univariable analysis OR (95% CI)	Multivariable analysis OR (95% CI)
Nontuberculous mycobacteria	20.00 (4.48-89.36)	11.24 (2.37-53.24)
Tuberculosis	1.86 (1.41-2.45)	1.29 (0.97-1.71)
CCI ≥1	1.89 (1.77-2.01)	1.83 (1.71-194)
Bronchiectasis	3.19(2.76-3.69)	2.74 (2.36-3.18)

Reference

1. Chen H-H, et al. Association between a history of mycobacterial infection and the risk of Sjögren's syndrome: a nationwide, population-based case-control study. OP0074. EULAR 2017.

Antiphospholid Syndrome

Due to the unpredictability and speed at which progression takes place, timely diagnosis of antiphospholid syndrome (APS) is crucial to improve the accuracy of the treatment. Recently, micro (mi) RNAs – modulated by aPL-IgG antibodies – have been identified as potential novel biomarkers for diagnosis and typifying of their atherothrombotic status.

Biomarkers

MiRNAs could be a useful tool in the prevention and management of the disease as was demonstrated by Arias-de la Rosa et al. The study which was conducted to identify suitable miRNAs included 90 APS patients and 42 healthy donors. Using a Polymerase Chain Reaction (PCR)-Array and Ingenuity Pathways analysis software (IPA), 39 circulating miRNAs differentially expressed were identified including 19 up-regulated and 20 down-regulated in APS. A total of 11 miRNAs was recognized as potential modulators of target genes involved in the physiopathology of APS. Logistic Regression and receiver operating characteristic (ROC) curve analyses identified a signature of 10 miRNA ratios as biomarkers for diagnosis of APS with great accuracy (Area under the Curve [AUC]:0.81), along with 2 miRNA ratios as biomarkers for typifying the atherothrombotic status of APS (AUC:0.76). Patients with thrombosis but without associated autoimmune disease displayed a specific miRNA profile, which was distinct from that of APS patients. The miRNA signature was related to clinical features of APS such as the occurrence of foetal loss and the type of thrombosis suffered. It also correlated with parameters linked to autoimmunity (aPL-IgG titers), inflammation, and thrombosis (ABI, ESR, TF, PAI-1, MCP-1, VEGF-A and VEGF-R1). In vitro treatment of monocytes and endothelial cells with aPL-IgG antibodies promoted a significant deregulation in the secreted levels of the selected miRNAs and atherothrombotic target proteins [1].

Reference

1. Arias-de la Rosa I, et al. Circulating microRNAs as biomarkers for diagnosis and typifying the atherothrombotic status in Antiphospholipid Syndrome. THU0218. EULAR 2017.

Systemic Lupus Erythematosus

A new biomarker in patients with systemic lupus erythematosus (SLE) who are asymptomatic for CVD is able to spot atherosclerosis in these patients. Furthermore, iron deficiency may play a significant role in fatigue which is often experienced by SLE patients. Interestingly, anifrolumab is associated with increases in Lupus Low Disease Activity State (LLDAS) attainment, as well as greater aggregate and sustained time in LLDAS.

Blood test to detect and heart attack risk in lupus patients without cardiovascular symptoms

Findings from a study by Divard et al. showed that the presence of the biomarker High Sensitivity Cardiac Troponin T (HS-cTnT) in lupus patients without symptoms of CVD who are considered to be at low risk of CVD based on traditional risk factors, is associated with the presence of atherosclerosis. Overall, the risk of atherosclerosis was increased by a factor of 8. The study was performed in 63 lupus patients in which 36.5% was found to have signs of carotid plaques compared to 11.1% in the control group. None of these patients nor the controls had symptoms of CVD; all of them also had a low Framingham risk factor score. Only age (P=0.006) and lupus disease status (P=0.017) were independently associated with the presence of carotid plaques. It was shown that 87% of lupus patients with carotid plaques had a detectable HS-cTnT whereas 42.5% of lupus patients without plaques had a detectable blood level of HS-cTnT (P<0.001). Conversely, 54.5% of lupus patients with a detectable HS-cTnT, but only 11.5% with an undetectable HS-cTnT, had a carotid plaque (P<0.001) [1].

Link iron deficiency and fatigue

Fatigue appears to be a common and debilitating symptom described by young patients with systemic lupus erythematosus (SLE). Wincup et al. investigated the relationship between early iron deficiency measured by red blood cell distribution (RDW) and fatigue in adolescents and young adults with SLE. Patients – with a median age of 20 years – were recruited prospectively between November 2016 and January 2017. Of the 33 included patients, 85% was female. It emerged that 36.3% of patients was anaemic (11 were female, 1 was male). An analysis of the sub-group of 21 non-anaemic patients found Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Score and RDW continue to show a statistically significant association (P=0.026; r=-0.49). The researchers concluded that standard serological and clinical markers of disease activity did not correlate with the burden of fatigue, but increased RDW has been shown for the first time to correlate with increased fatigue in patients with lupus. These findings suggest that iron deficiency may play a significant role in the manifestation of this troublesome symptom. The next step is a planned trial of therapeutic iron infusions as part of the treatment of fatigue in SLE [2].

Table 14 Requirements for LLDAS [15]

SLE Disease Activity Index (SLEDAI)–2K <4 without major organ activity
No new disease activity
Physician Global Assessment (PGA; 0–3) ≤1
Prednisolone ≤7.5 mg/day
Tolerance of standard immunosuppressant dosages

Anifrolumab: post-hoc analysis of MUSE trial

The post-hoc analysis of the 52-week MUSE trial – which assessed anifrolumab in patients with moderate to severe SLE – evaluated Lupus Low Disease Activity State (LLDAS) as a randomized controlled trial (RCT) endpoint [3]. Patients with active SLE received IV placebo, anifrolumab 300 mg, or 1,000 mg, in addition to standard of care, every 4 weeks for 48 weeks. The LLDAS requirements are outlined in Table 14. The results showed that patients treated with placebo (N=102), anifrolumab 300 mg (N=99), or anifrolumab 1,000 mg (N=104), LLDAS criteria were met at least once by 35%, 52%, and 46% of patients, respectively. Positive associations were observed between LLDAS and both the SLE Responder Index (SRI) [4] and BILAG-based Composite Lupus Assessment (BICLA), with 87% and 74% of patients attaining LLDAS at week 52 also being SRI (4) and BICLA responders, respectively. However, only 47% and 51% of SRI (4) and BICLA responders reached LLDAS. Increased LLDAS attainment from week 12 (300 mg) or 28 (1,000 mg) was associated with anifrolumab treatment, compared with placebo (OR range; 300 mg: 1.7-3.6; 1,000 mg: 1.7-2.5). LLDAS was attained earlier in anifrolumab-treated patients. At week 52, more anifrolumab-treated patients attained a LLDAS and more anifrolumab-treated patients spent ≥50% of observed time in LLDAS. The OR of sustained LLDAS for at least six consecutive visits from week 12 to 52 was 4.02 for patients on 300 mg and 2.95 for patients on 1,000 mg. It was concluded that LLDAS is associated with validated treatment response measures, SRI(4) and BICLA, but is more stringent than either. Anifrolumab was associated with a ≤3.6-fold OR increases in LLDAS attainment, as well as greater aggregate and sustained time in LLDAS. Researchers pointed out that this LLDAS definition should be considered as a study endpoint in SLE randomized controlled trials (RCTs) [5].

References

1. Divard G, et al. High sensitivity Cardiac Troponin T is a biomarker for atherosclerosis in Systemic Lupus Erythematous patients: a cross-sectional controlled study. OP0319. EULAR 2017.
2. Wincup C, et al. Identifying the links between iron deficiency and fatigue in adolescents and young adults with Systemic Lupus Erythematosus. THU0265. EULAR 2017.
3. Furie R, et al. Arthritis Rheumatol. 2017;69:376-86.
4. Franklyn K, et al. Ann Rheum Dis. 2015;75:1615-21.
5. Morand E, et al. the Lupus Low Disease Activity State (LLDAS) definition discriminates responders in a Systemic Lupus Erythematosus (SLE) trial: post-hoc analysis of the phase IIb MUSE trial of anifrolumab. OP0001. EULAR 2017.

Vasculitis

The major organs targeted by antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are the kidneys. A comparison of the clinical features of AAV with renal involvement with those of patients without renal involvement show some remarkable differences. However, rituximab treatment does not seem to make a difference with regard to safety between granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) patients.

ANCA-associated vasculitis with renal involvement

Prognosis in ANCA vasculitis was studied in 122 patients in Japan by Fukui et al. As expected, patients with renal involvement did worse; they were also older and had lower levels of C3 (the latter associated with increased mortality). The C4 levels did not differ between the poor and good prognosis groups. These findings were obtained by an observational study of 104 patients with associated vasculitis (AAV). Of those, 12 had eosinophilic GPA, 23 GPA, 66 microscopic polyangiitis, and 3 renal limited vasculitis. A total of 69 patients had renal involvement; they had a higher median age at diagnosis than patients without renal involvement group (75 years vs 66 years, P<0.001). Patients with renal involvement included fewer GPA patients compared to other AAV types. Patients with renal involvement had lower hemoglobin levels (10.3 g/dL vs 12.3 g/dL) and lower platelet levels (23.7x104/μL vs 28.7x104/μL). Patients with renal involvement had higher erythrocyte sedimentation rate (78mm/h vs 20mm/h), MPO-ANCA titers (116 U/mL vs 58 U/mL) and urine protein levels (0.81 g/gCr vs 0.15 g/gCr). Patients with renal involvement had lower C3 levels, but CH50 and C4 levels did not differ between in two groups. There were no differences in treatments including doses of prednisolone and use of methylprednisolone pulse and cyclophosphamide between in two groups. Multivariable regression analysis revealed that age at diagnosis is the most significant explanatory variable to renal involvement. It emerged that 19% of patients with renal involvement had initiations of dialysis. Multivariable analysis demonstrated estimated glomerular filtration (eGFR) rate at diagnosis is the most significant explanatory variable to initiations of dialysis (P=0.010). Receiver operating characteristic curve showed the cut-off level of the eGFR rate to distinguish initiations of dialysis was 37mL/min/1.73m2 (sensitivity=79%, specificity=70%, AUC=0.80). Assessed by a log-rank test, the overall survival (OS) rate did not differ between the two groups (P=0.29) [1].

Rituximab: interim-analysis of safety ANCA-associated vasculitis registry

Niles et al. characterized safety events in an observational registry of patients with GPA or MPA who initiated rituximab. The results of the interim-analysis of safety events included SIs, infusion-related reactions (IRRs), serious cardiac events, malignancies, and other serious events. A total of 97 patients (totaling 291 patient-years) received rituximab, of whom 70% received rituximab retreatment. The median follow-up was 2.4 years and 91% of patients was ANCA-positive whereas 78% had GPA. The researchers found that 33 patients experienced 71 SAEs (32.4/100 patient-years; 11 patients had 20 SIs, 9 patients had 13 serious CV events 12 of which were reported as unrelated to rituximab). Of the 13 CV events, 9 were atrial arrhythmias and most patients had associated renal or CV disease history. No serious IRRs or SAEs within 24 hours of rituximab infusion were observed. A total of 6 fatalities was observed with causes of death including septic shock, interstitial lung disease (ILD), CHF, cardio-respiratory arrest and 2 deaths of unknown etiology. The severe disease flare rate was 5.94/100 patient-years. Among patients who received rituximab retreatment, the IRs of SAEs and SIs were not increased compared with the overall cohort. It was concluded that SAEs were not increased compared with comparable cohorts of patients with renal involvement, and that the safety events did not increase with rituximab retreatment. These results are consistent with the known safety profile of rituximab and provide preliminary long-term, practice-level safety data for the use of rituximab in GPA/MPA [2].

References

1. Fukui S, et al. Clinical features and prognosis of ANCA-associated vasculitis with renal involvement at diagnosis. THU0303. EULAR 2017.
2. Niles J, et al. Safety following initiation of rituximab in granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA): interim analysis of the rituximab in ANCA-associated vasculitis registry (RAVER). THU0301. EULAR 2017.

Scleroderma

Nailfold videocapillaroscopy is able to detect early systemic scleroderma (SSc) patterns; a specific blood test which can be used to diagnose SSc can also aid diagnosis. Nevertheless, treatment strategies can be complex and real-life feedback on the use of these provide valuable practical guidance. Rituximab seems to be a promising long-term treatment in SSc.

New tools for early diagnosis

A large scale study which was conducted in 40 centres involving 1,085 patients with Raynaud's phenomenon has demonstrated that patients who meet very early diagnosis of SSc (VEDOSS) criteria predominantly have the characteristic appearance of an early SSc pattern when investigated with nailfold videocapillaroscopy. This is a non-invasive, inexpensive and reproducible imaging method which allows the evaluation of structural changes in the peripheral microcirculation. The combination of a microscope with a large magnification lens coupled with a digital video camera aided by specific software allows for a precise measurement of the morphology of capillaries and their density [1]. The prevalence of nailfold videocapillaroscopy early SSc patterns was higher in the Anti-Nuclear Antibody (ANA) positive VEDOSS patients than in those without. The estimated distribution of early SSc patterns was 40% vs 13% in the ANA-positive and ANA-negative patients, respectively. A typical 'early' pattern was present in 79% of 'target' patients. For the quantitative capillaroscopic characteristics, the only statistically significant difference between the ANA-positive and ANA-negative patients was the presence of 'moderate' or 'extensive' giant capillaries (23% vs 5%, P=0.027) [2]. Another new tool to aid diagnosis in patients suspected of having SSc is the epitope-based blood test which was designed to detect SSc-specific autoantibodies. Previous studies have identified a specific epitope (PDGFRα) which is recognised by autoantibodies in patients with SSc. Peptides making up this epitope have been shown to be specifically recognised by an immunoglobulin (IgG) in the blood of patients with SSc, but not of controls. In an Italian study, one of these peptides – a so-called 'immunodominant peptide' – has been used to develop a specific blood test which can be used to diagnose SSc. The first step in this new study involved the identification of one specific peptide that could effectively discriminate SSc from healthy control blood samples from a large PDGFRα peptide library, which had been used for epitope mapping of monoclonal anti-PDGFRα antibodies among a population of 25 SSc and 25 healthy control blood samples. Then, using a second smaller PDGFRα peptide library, the identity of this one immunodominant epitope was confirmed. Statistical analysis identified two subgroups of SSc samples: reactive vs nonreactive, the latter undistinguishable from the healthy controls. A third peptide library was then used to identify the peptide recognised exclusively by the reactive SSc blood samples, taken from patients with active, progressive disease, whereas the nonreactive SSc samples were taken from subjects with less active, non-progressive disease [3].

Prevalence of FAM111B gene mutations

The genetic basis of SSc is still unclearly characterized. Implicated genes have been associated with autoimmune dysregulation with relatively few variants associated with fibrosis [4]. Geclu et al. discovered that mutations in FAM111B gene cause hereditary fibrosing poikiloderma with tendon contractures, myopathy, and pulmonary fibrosis (POIKTMP) [5] which is a multisystem fibrotic condition with clinical aspects of SSc [6]. This observation has established FAM111B as a candidate gene for SSc and the next step was to assess whether FAM111B gene mutations are present in SSc patients as well as further exploring relationships between FAM111B mutations and clinical expression of SSc. A total of 131 SSc patients was genotyped (men N=13; women N=118, mean age 26.6 years and mean age of symptom onset at 25.3 years). Just over half of the (South-African) patients were black and 72% had diffuse systemic sclerosis (DSSc) with a median modified Rodnan skin score (mRSS) of 11. In 8 patients, 7 rare genetic variants were found: C832G>A; C855G>T; C917A>G; C937G>A; C988C>T; C995A>C and C1006G>C. These variants were missense mutations of unknown significance with a minor allele frequency <0.01. No FAM111B mutations causing POIKMT were found in patients with SSc. In summary, rare genetic variants of unknown significance (GVUS) in FAM111B gene were found in patients with SSc. It is possible that the GVUS may modify the function of FAM111B, and influence the pathogenesis of SSc or that they are rare polymorphisms without functional impact [7].

Real-life treatment strategies

The number of second line treatment options for SSc are (still) limited, and choosing the order of treatment is not yet supported by a wide range of data. The SSc treatment algorithms were updated recently (based on SSc experts' daily practice) by Fernández-Codina et al. An initial survey based on the 2012 algorithms was designed which enquired if so and which changes should be considered. The questionnaire had a 67% response and was conducted between August and October 2016 (Table 15) [8]. Thus, some disagreement for the 2nd line treatment of SSc remains. Combinations of PDE5i and ERA are prescribed now in mild PAH treatment and prostanoids have been incorporated as 3rd line agents in active DU treatment. MMF is the new 1st line treatment for ILD induction and rituximab the 3rd. IV CYA and ASCT were recommended as 3rd and 4th line treatments in patients with severe skin involvement whereas rituximab and tocilizumab have been incorporated in the treatment of inflammatory arthritis treatment. These new insights may guide therapy in SSc [8]

Rituximab: long-term treatment

It has been suggested by preliminary data that rituximab may be successfully used in SSc patients. Its efficacy and long-term effects were evaluated in a study including 15 SSc patients who had a mean age of 52.7 years and mean disease duration of 10.3 years. They were treated with one or more cycles of rituximab (4 weekly infusions of 375 mg/m^2); all patients received rituximab repeatedly every 6 months for a total of 2-6 cycles. The first 6 months after rituximab treatment, the extent of skin sclerosis measured with mRSS significantly improved from 17.3 to 13.4 (P<0.01). It remained stable at the end of the follow-up (13.3; P=0.009). The usefulness of rituximab on skin sclerosis was more evident in patients with diffuse cutaneous SSc (N=10) as is showed a significant decrease of mRSS after the first 6 months (from 24.2 to 18.1; P=0.006) as well as at the end of the follow-up period (18.0; P=0.005). Also, improvements in hypermelanosis (12/12 patients), pruritus (11/13 patients), and calcinosis (3/6 patients) were observed. Moreover, arthritis revealed particularly responsive to rituximab treatment leading to a clear-cut reduction of swollen and tender joints in 12/13 patients. Lung fibrosis detected in 12/15 patients remained stable during the entire follow-up. These positive clinical changes were mirrored by the subjective improvement of patients' wellbeing in all cases. No significant side effects were observed. The research team concluded that this study reinforces the previous trials showing the usefulness of rituximab in the management of SSc patients, along with its good safety profile. The specific therapeutic activity of rituximab, able to down-regulate the B-cell over expression, might explain its beneficial effects on some SSc clinical manifestations, in particular the improvement of both skin sclerosis and articular involvement, along with the possible stabilization of lung fibrosis [9].

Table 15 Outcomes questionnaire on SSc treatment [8]

	% respondents who agreed with previous algorithms	Previous algorithm	New proposal(s) if applicable
Scleroderma renal crisis (SRC)	65-69%	1st line: angiotensin converting enzyme inhibitors (ACEi) 2nd/3rd adding: calcium channel blockers (CCB) or angiotensin receptor blockers (ARB) 4th line: alpha-blocker	--
Mild pulmonary arterial hypertension (PAH)	45%		The majority suggested first phosphodiesterase 5 inhibitors (PDE5i) or endotelin receptor antagonists (ERA) + PDE5i, then prostanoids.
Severe PAH	65%	1st: prostanoids 2nd ERA + PDE5i 3rd ERA + prostanoids	
Mild Raynaud's phenomenon (RP)	66%	1st CCB 2nd adding PDE5i 3rd ARB or switching to another CCB 4th prostanoids	
Severe RP	52%	1st CCB 2nd adding PDE5i 3rd ERA 4th prostanoids	
Active digital ulcer (DU) treatment	40%	1st CCB 2nd PDE5i 3rd prostanoids	
ILD	24% (induction) 65% (maintenance)	Maintenance: 1st: mofetil mycophenolate (MMF) 2nd: azathioprine 3rd: IV CYP 4th: oral CYP	Induction: 1st: MMF 2nd: IV cyclophosphamide (CYP) 3rd: rituximab
Skin involvement	57% (mRSS of 10)	Mrss 10? 1st: methotrexate 2nd: MMF mRss 24? 32% suggested: 1st: MMF 2nd: methotrexate mRSS 32? 36% chose: 1st: methotrexate 2nd: MMF 3rd: IV CYP 4th: autologous stem cell transplantation (ASCT)	
Inflammatory arthritis	45%		1st: methotrexate 2nd: low dose steroids 3rd: hydroxychloroquine, 4th: rituximab or tocilizumab

References

1. Souza EJ, Kayser C. Nailfold capillaroscopy: relevance to the practice of rheumatology. Rev Bras Reumatol. 2015;55(3):264-271.
2. Cutolo M, et al. Preliminary analysis of nailfold capillaroscopy in the very early diagnosis of systemic sclerosis (VEDOSS): the CAPI-VEDOSS experience. OP0035. EULAR 2017.

3. Moroncini G, et al. Development of a novel epitope-based diagnostic assay for systemic sclerosis. OP0031. EULAR 2017.
4. Romano E, et al. The genetics of systemic sclerosis: an update. Clin Exp Rheumatol. 2011. 29(2 Suppl 65): S75–86.
5. Mercier, S, et al. Mutations in FAM111B cause hereditary fibrosing poikiloderma with tendon contracture, myopathy, and pulmonary fibrosis. Am J Hum Genet. 2013. 93(6):1100–7.
6. Khumalo NP, et al. Poikiloderma, tendon contracture and pulmonary fibrosis: a new autosomal dominant syndrome? Br J Dermatol. 2006;155(5):1057-61.
7. Gcelu A, et al. Prevalence of FAM111B gene mutations in systemic sclerosis FRI0379. EULAR 2017.
8. Fernández-Codina A, et al. Real-life treatment strategies for systemic sclerosis according to experts. FRI0375. EULAR 2017.
9. Lumetti F, et al. Long-term treatment with rituximab in Systemic Sclerosis patients: update of our clinical experience. FRI0388. EULAR 2017.

Osteoarthritis and Osteoporosis

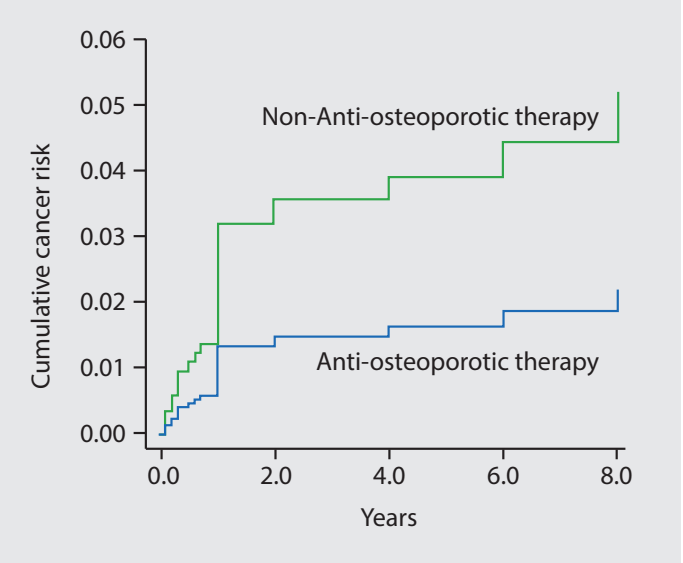
Biomarkers for osteoporosis and novel imaging techniques

It has been revealed that adiponectin levels depend on osteoporosis presence in RA patients, and determination of adiponectin may be a useful laboratory marker for the diagnosis of osteoporosis. Polyakova et al. studied 88 women with documented diagnosis of RA and mean disease duration of 6.56 years, using EULAR/ARA 2010 criteria to diagnose the patients. Female patients with II degree of disease activity (DAS28), Steinbrocker stage II (erosive), rheumatoid factor- and anti-cyclic-citrullinated peptide antibody (CCP)-positive were prevalent. Patients who had surgery or developed an infection within the last 8 weeks, pregnant and breast-feeding women, those with severe heart, liver or kidney disease, immune deficiency, leukopenia or chronic infection were excluded. A control group of 45 healthy females aged 25-59 years were included in the study. Both groups were adjusted for age (P>0.05) and showed no statistically significant differences. Serum adiponectin levels (µg/ml) using Human Adiponectin ELISA commercial test systems were measured; in the control group, these were 12.5±0.9 µg/mL whereas in patients with osteoporosis and RA, these were significantly higher (P<0.001). Mean serum adiponectin levels in RA patients with normal BMD and without osteoporosis were 35.21 µg/ml; mean serum adiponectin levels in RA patients with osteoporosis were 52.42 µg/ml. These findings led to the conclusion that adiponectin levels of ≥44 µg/mL were associated with osteoporosis whereas adiponectin levels ≤43.9 µg/mL indicated a normal BMD [1].

Lower cancer risk with anti-osteoporotic therapy in osteoporotic vertebral fractures

To date, it has been unclear what the long-term effect of anti-osteoporotic therapy on cancer risk is. Chen et al. determined the influence of anti-osteoporotic therapy on cancer risk in patients with osteoporotic vertebral fracture by means of a retrospective study. Anti-osteoporotic therapy consisted of alendronate, ibandronate, zolendronic acid, raloxifen, teriparatide, and denosumab). A total of 1,128 patients with acute vertebra fractures were enrolled of which 693 patients accepted anti-osteoporotic therapy and 432 did not. The mean age of the patients who received anti-osteoporotic therapy was 73.86 years compared to 72.82 in patients who did not have anti-osteoporotic therapy. The researchers found that 2.2% patients with anti-osteoporotic therapy developed cancer, while 5.6% of patients who did not use anti-osteoporotic therapy developed cancer (P=0.004). After adjusting for potential confounders, patients with anti-osteoporotic therapy still had a lower cancer risk (P=0.038; HR 0.428, Figure 4). Unsurprisingly, smoking increased the cancer risk significantly (P=0.002; HR 10.505)The results thus show that anti-osteoporotic therapy decreases cancer risk which means these drugs can safely be used in osteoporotic management [2].

Figure 4 Risk of cancer with (non)osteoporotic therapy [2]



New therapies for osteoporosis

Currently, anti-resorptive drug therapy is the cornerstone of fracture prevention. Anti-resorptive drugs decrease bone remodelling, allowing the remaining bone to increase secondary mineralisation, and – with denosumab – also allowing periosteal bone modelling. The only available bone-forming drug currently available is teriparatide. It increases bone formation more than bone resorption, and has been shown to reduce the risk of vertebral and non-vertebral fractures. However, 2 randomized clinical trials have been published recently, describing the effect of new bone forming agents on the risk of fracture. The first agent is abaloparatide, a 1–34 fragment of parathyroid hormone-related protein (PTHrP) with different pharmacokinetics and potential different signalling mechanisms compared to teriparatide. It increases bone formation more than bone resorption, both to a lesser degree than teriparatide. In the double blind, randomised placebo-controlled 18-month ACTIVE study, abaloparatide significantly reduced the risk of vertebral (-86%), clinical (-43%), non-vertebral (-43%) and major fractures (-70%). When compared to teriparatide in a parallel randomised exploratory open-label comparison, bone density increased significantly more with abaloparatide, but the anti-fracture effect was similar, except for a significantly better result on prevention of major fractures. Another new agent in osteoporosis is romosozumab, a monoclonal antibody which binds sclerostin, an inhibitor of bone formation. Contrarily to other bone forming agents, romosozumab disconnects the increase in bone formation from a decrease in bone resorption. The FRAME study showed that romosozumab significantly reduced the risk of vertebral (-63%) and clinical fractures (-36%) during the first year. This effect was maintained by transitioning to one-year denosumab treatment. Although the effect on non-vertebral fractures was not significant, a geographic interaction was found which may explain this effect. When South-American patients were excluded – in whom the fracture risk was low – 1-year treatment with romosozumab significantly decreased the risk of non-vertebral fractures by 42% [3].

Romosozumab: rapid and large reductions in vertebral fracture risk

Twelve months treatment with romosozumab was associated with rapid and large reductions in the risk of a vertebral fracture compared to placebo in postmenopausal women with osteoporosis. All clinical vertebral fractures occurred in the first 2 months of treatment; overall, the risk of a vertebral fracture was more than 5 times greater in the group of women who were given placebo. This was demonstrated by the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME), an international, randomised, double-blind, placebo-controlled, parallel-group trial. FRAME enrolled 7,180 postmenopausal women (aged between 55-85 years) with evidence of osteoporosis confirmed by abnormally low BMD scores in spine, hip, and femoral neck, but no severe vertebral fracture. Patients received monthly romosozumab (N=3,589) or placebo (N=3,591) for 12 months. Of 119 women reporting back pain over 12 months, 20 were diagnosed with a new or worsening vertebral fracture. In the romosozumab group, there were 3 clinical vertebral fractures (<0.1% of patients and all in the first 2 months) compared to 0.5% with placebo. Clinical vertebral fracture risk was 83% lower in the romosozumab group vs placebo at 12 months. In women with clinical vertebral fracture vs no clinical vertebral fracture, measurements of BMD showed more severe osteoporosis. However, other baseline characteristics were comparable among all women who reported back pain in both treatment groups [4].

Denosumab: efficacy and safety in post-menopausal osteoporosis and in cancer: a systematic review and meta-analysis

The safety of denosumab – a receptor activator of nuclear factor kappa (RANK) ligand antibody – has been assessed by Aubailly et al. by means of a literature review. A total of 6,136 articles was of potential interest, of which 19 met the inclusion criteria; 7 articles compared the safety of denosumab to bisphosphonates in post-menopausal osteoporosis. With regard to any AEs, there were no significant differences when comparing denosumab with bisphosphonates (relative risk [RR] 0.98), and SAEs (RR 1.04). When denosumab was compared with placebo, no significant difference was seen in postmenopausal osteoporosis in any AE (RR 0.98), and SAE (RR 1.03), although cellulitis was more frequently found with denosumab (RR 8.03) No cases of osteonecrosis of the jaw had been reported. Also, 5 articles were pooled to compare denosumab with bisphosphonates in patients with bone metastases and no significant difference was found in any AE (RR 0.99), SAE (RR 0.99), and osteonecrosis of the jaw (RR 1.40). A comparison was also performed between patients treated with placebo or denosumab in breast and prostate cancer without bone metastases (4 articles were available). Although no significant difference was found in any AE (RR 1.01), the use of denosumab was associated with a significantly increased risk of hypocalcemia (RR 5.20) and of cholecystitis (RR 3.43). It was concluded that denosumab had a relatively good safety profile in post-

menopausal osteoporosis, although significantly more cellulitis occurred when compared with placebo. Also, denosumab was associated with more hypocalcemia and cholecystitis than placebo in cancer patients [5].

References

1. Polyakova Y, et al. new biomarker for diagnosis of osteoporosis in rheumatoid arthritis patients. FRI0554. EULAR 2017.
2. Chen Y.-C, et al. Anti-osteoporotic therapy decreases cancer risk in patients with Osteoporotic vertebral fractures. FRI0526. EULAR 2017.
3. Geusens P, et al. Emerging therapies for osteoporosis. SP0027. EULAR 2017.
4. Geusens P, et al. Romosozumab rapidly reduces clinical vertebral fracture incidence: results from the FRAME study. OP0048. EULAR 2017.
5. Aubailly M, et al. Safety of denosumab in post-menopausal osteoporosis and in cancer: a systematic review and meta-analysis. FRI0561. EULAR 2017.

Fibryomalgia

Fibromyalgia is a chronic primary pain syndrome which is characterized by widespread pain and major comorbidities. The condition seems to be caused by a combination of factors of which predisposition - thought to be highly influenced by traumatic events during childhood - and an initiating painful event are the main triggers.

Background and comorbidities of fibromyalgia

Fibromyalgia can be distinguished from other chronic widespread pain by tender point counts (American College of Rheumatology 1990 criteria), or psychosocial distress (ACR 2010). However, both these ACR definitions are problematic for research purposes as the mechanisms of tender points are poorly understood, and the use of distress as an inclusion criterion can be problematic. Chronic primary pain is characterized by significant emotional distress and functional disability which can be extremely debilitating for the patient. Many factors are thought to be involved: biological, psychological as well as social factors contribute to the pain syndrome. The diagnosis is appropriate independently of identified biological or psychological contributors unless another diagnosis would better account for the presenting symptoms. The location of chronic primary pain can be anywhere on the body (face, low back, neck, upper limb, thorax, abdominal, pelvis, urogenital region), or in a combination of body sites (widespread pain). It can be stated that generally, multiple sites of pain are associated with higher distress and disability than single sites. Chronic primary pain is also often associated with sleep disturbance, adverse side effects of treatments (such as medication dependence), and comorbidities (such as depression, anxiety, anger, guilt, fear, and a range of chronic medical conditions). Treede et al. compared the pathophysiology of fibromyalgia, other chronic widespread pain and chronic localized pain in the lower back. It was shown that fibromyalgia patients had a higher comorbidity of anxiety and depression and more functional impairment than the other groups [1]. A deficit in conditioned pain modulation (CPM) was related to the spatial spread of ongoing pain, which was consistent with the neurobiology of endogenous pain control systems. Fibromyalgia and chronic widespread pain differ when it comes to psychosocial burden, which is consistent with the shift in clinical diagnostic criteria. Tender point counts (an evoked pain measure) were still useful to identify the fibromyalgia patients [2]. A study using the childhood trauma questionnaire suggests that early stress exposure is associated nonspecifically with lowered pressure pain thresholds which may be related to tender points [3]. Experimental sleep deprivation in healthy subjects or rodents leads to symptom profiles reminiscent of fibromyalgia (e.g. widespread hyperalgesia, anxiety), suggesting a potential vicious circle of pain, hyperalgesia and sleep disturbance in fibromyalgia [4].

References

1. Gerhardt A, et al. Clin J Pain. 2016;32:568–579.
2. Gerhardt A, et al. Pain. 2017. In press.
3. Tesarz J, et al. Pain. 2106;157:1799-1809.
4. Treede R.-D, et al. Signs, symptoms and co-morbidities of fibromyalgia. SP0019. EULAR 2017.