Table 1. Demographics and Baseline Characteristics

Variable	Category	Non-Obese (n=95)	Obese (n=83)	P-value
Sex	Female	61 (64%)	66 (80%)	**0.02**
	Male	34 (36%)	17 (20%)	
Age		53±12	50±13	0.08
Duration disease		8 [6, 11]	12 [7, 14]	**<0.001**
Rheumatoid factor	Negative	20 (21%)	60 (72%)	**<0.001**
	RF	12 (13%)	8 (10%)	
	CCP	17 (18%)	0 (0%)	
	RF/CCP	46 (48%)	15 (18%)	
CRP		35 [10, 51]	24 [7, 40]	**0.02**
ESR		37 [14, 59]	28 [17, 45]	0.57
MTX		15.5±9.2	13.5±9.6	0.15
Administration	Infusion	4 (4%)	5 (6%)	0.74
	Subcutaneous	91 (96%)	78 (94%)	
DAS pre-treatment		5.6±0.7	5.4±0.8	0.06

Results suggested that there were significant differences between two groups for sex, duration of disease, RF and CRP. There was also some evidence of difference between groups in terms of their age and pre-treatment DAS28 score but these differences were only of borderline statistical significance. There was smaller proportion of males in the obese group with 20% male compared to 36% of non-obese patients. Obese patients had on average a longer disease duration with a median of 12 years compared to a median of 8 years for the non-obese group. The RF status also varied between groups with a much higher proportion of patients in the negative category for the obese group. CRP values were significantly lower in the obese group with a median of 24 compared to 35 in the non-obese group.

Table 2. EULAR response between obese and non-obese patients

EULAR response	Non-Obese N (%)	Obese N (%)	P-value
No response	9 (9%)	32 (39%)	<0.001
Moderate response	40 (42%)	36 (43%)	
Good response	46 (48%)	15 (18%)	<0.001
	Non-Obese (n=95), Mean ± SD	Obese (n=83), Mean ± SD	
DAS28 post-treatment	3.2±1.0	4.2±1.3	
DAS28 reduction	2.4±1.3	1.1±1.3	

Non-obese had the best response with 48% good response compared to18% of the non-obese group with post treatment mean DAS28 score of 3.2 and mean reduction of 2.4.

Conclusions: Obesity is important factor that impacts treatment and outcome in RA. Future clinical studies to elucidate the pharmacokinetics of specific biologic agents in relation to BMI should provide further clinical guidance.

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SAT0141 OPTIMAL CIRCULATING ADALIMUMAB LEVELS RANGE ASSOCIATED WITH GOOD CLINICAL RESPONSE IN RHEUMATOID ARTHRITIS PATIENTS

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Background: TNF inhibitors have become an important part of healthcare worldwide for inflammatory diseases such as RA[1]. Many publications show that responding patients have higher Adalimumab (Ada) serum trough levels (ATL) than non-responders. These factors are influenced by age, weight, gender or pharmacokinetics, which in turn depend on immunogenicity. Concomitant use of immunomodulators such as methotrexate (MTX) reduces immunogenicity and enhances therapy benefits[1,3].Increasing drug dosage in patients with less response is the standard practice, while lowering dosage is advisable in patients achieving remission. Many recent publications[2] assess serum trough levels that reflect optimal response and which could be used as benchmark for guidance to implement the Therapeutic Drug Monitoring.

Objectives: To establish an optimal Ada serum trough level (ATL) range in RA patients associated with good clinical response.

Methods: A prospective observational study with 40 RA patients under Ada treatment recruited in the Rheumatology Unit of Universitary Hospital La Paz was conducted. Demographic data, ATL and clinical activity of patients treated with 40 mg/kg every other week from 4 months up to 12 years of treatment were collected. A total of 206 samples were analyzed [χ=5 (3–13) samples/patient]. Disease activity was assessed using the DAS28 index and clinical improvement with $\triangle$DAS28. ATL were measured with a capture ELISA[3] [correlation with Promonitor (Derio, Vizcaya, Spain) k=1, r=0.91; and with Sanquin (Amsterdam, The Netherlands) k=1, r=0.86] and statistical analysis were performed with GraphPadPrism 5.0 software.

Results: Demographic data of our cohort were: mean age (±SD) 56.75±16.06, with 82.5% of females and 45% of patients treated with concomitant MTX. Sixty-five and 72% of patients were RF and ACPA positive, respectively. ATL were similar in patients treated with concomitant MTX (χ=3.82±2.42 μg/ml) or Ada monotherapy (χ=3.54±2.43 μg/ml) p=0.81.

Consistent with previous studies[1,2], low-disease activity patients (DAS28$\leq$3.2) presented higher Ada circulating levels than patients with high-disease activity [3.7 μg/ml (IQR 2.97–5.48) vs. 1.71 μg/ml (IQR 0.23–4.51), p=0.01]. The median of Ada levels excluding the values (n=6) that showed immunogenicity was 3.42 μg/ml (IQR 1.55–5.03) where 3.50 μg/ml represented the most frequent value (15% of patients). Lack of clinical improvement ($\triangle$DAS$<$1.2) was linked to drug levels below percentile 25 (p=0.04) whilst Ada levels above percentile 75 did not ensure more clinical improvement (p=0.7) than the values around the median.

Conclusions: ATL correlate with the disease activity and with the clinical improvement. The optimal range associated with good therapeutic response after the standard dose is *1.5–5 μg/ml*. Higher circulating drug levels do not entail better response, which indicates they could be unnecessary. The knowledge of the optimal drug ranges can guide the Personalized Drug Therapy in order to maximise effectiveness and minimise costs.

References:

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[3] Pascual- Salcedo, D. Rheumatology (Oxford), 2011.

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SAT0142 PREDICTORS OF INADEQUATE RESPONSE AND RAPID RADIOGRAPHIC PROGRESSION IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS RECEIVING METHOTREXATE: A POST HOC ANALYSIS OF 2 RANDOMIZED, CONTROLLED TRIALS OF ADALIMUMAB

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Background: Methotrexate (MTX) is recommended as first-line therapy in patients (pts) with rheumatoid arthritis (RA).[1] However, information is limited regarding factors that may predict a poor response to MTX.

Objectives: To identify predictors of MTX insufficient response (IR) and rapid radiographic progression (RRP) among pts with early RA receiving 6 months (mos) of MTX therapy.

Methods: In OPTIMA, pts with RA $<$1 year were randomized to receive either adalimumab (ADA) 40 mg every other wk (EOW) + MTX weekly (wkly) or placebo (PBO) EOW + MTX wkly for 26 wks. In PREMIER, pts with RA $<$3 years were randomized to receive ADA 40 mg EOW + MTX wkly, ADA 40 mg EOW + PBO wkly, or PBO EOW + MTX wkly for 2 years. This post hoc analysis compared MTX-IR pts, defined as not reaching stable low disease activity at wks 22 and 26 in OPTIMA and wks 20 and 24 in PREMIER, with pts who responded to initial MTX monotherapy. Comparisons were also made between pts who did and did not have RRP, assessed by an increase in modified Total Sharp Score (mTSS) of $>$1.5 from baseline (BL) to 6 mos. In pts with available data, backward logistic regression was used to identify potential predictors of MTX-IR and RRP. Candidate predictors included BL demographics, time-averaged disease parameters for 3 time intervals (through 4 wks, 8 wks, and 12 wks of MTX exposure), and BL disease characteristics for the 12-wk interval. Time-averaged variables were calculated as area under the curve standardized for length of time interval.

Results: This analysis included 525 MTX-IR and 162 MTX responders. Mean disease duration at BL was 6 mo for both groups. The mean Disease Activity Score 28 (C-reactive protein; DAS28[CRP]) was 6.2 vs 5.6, Health Assessment Questionnaire Disability Index (HAQ-DI) was 1.6 vs 1.3, and mTSS was 15.5 vs 12.2 for MTX-IR vs MTX responders, respectively. 171 pts experienced RRP, while 499 pts had no RRP; the mean disease duration at BL was 6 mo for both groups. The mean DAS28(CRP) was 6.4 vs 6.0 and HAQ-DI was 1.6 vs 1.5 for pts experiencing RRP vs pts who did not experience RRP, respectively. Mean mTSS at BL was higher for pts who experienced RRP (20.7) vs those who did not (12.4). Predictors of MTX-IR and RRP at 6 mos are shown in the Figure. Time-averaged HAQ-DI and DAS28(CRP) through 12 wks were the strongest predictors of both MTX-IR and RRP. Additionally, early clinical response (time-averaged DAS28[CRP]) at both 4 and 8 wks was predictive of both MTX-IR and RRP; however, time-averaged HAQ-DI was not predictive until wk 12.

Conclusions: In the OPTIMA and PREMIER trials, post-BL measures of RA activity appeared to be the strongest predictors of subsequent MTX-IR and of RRP. Pts who are likely to progress on MTX or have RRP may be good candidates for switching to earlier step-up therapy to reduce the likelihood of permanent bone damage.

References:

[1] Singh JA, et al. Arthritis Care Res (Hoboken). 2016;68(1):1–25.

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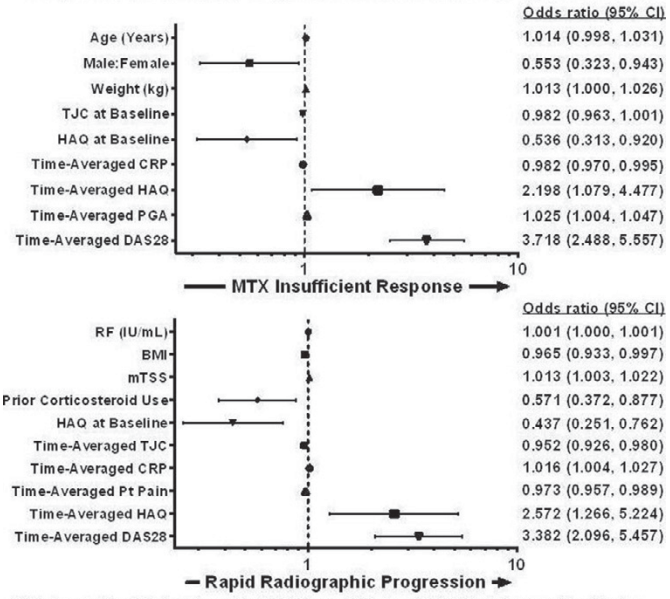
Figure. Predictors of Methotrexate Insufficient Response or Rapid Radiographic Progression in Patients with Early Rheumatoid Arthritis Receiving Methotrexate[A]



BMI, body mass index; CRP, C-reactive protein; DAS28, Disease Activity Score 28; HAQ, Health Assessment Questionnaire; mTSS, modified Total Sharp Score; MTX, methotrexate; PGA, Physician Global Assessment of disease activity; Pt pain, patient's assessment of pain; RF, rheumatoid factor; TJC, tender joint count.
[A]Time-averaged value through week 12 are shown.

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SAT0143 COMPARISON OF TREATMENT WITH GOLIMUMAB AND CERTOLIZUMAB-PEGOL IN ARTHRITIS- RESULTS FROM THE SOUTH SWEDISH ARTHRITIS TREATMENT GROUP (SSATG) REGISTER

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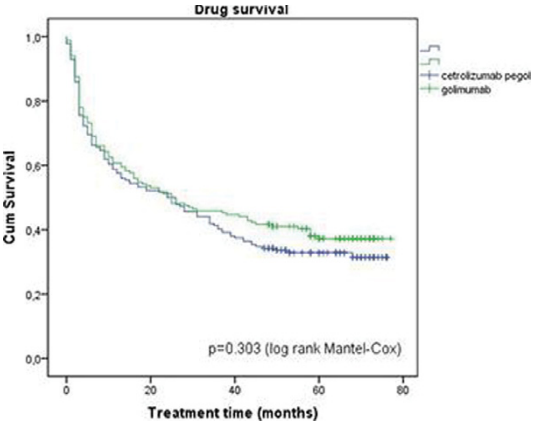
Background: "Head to head" studies comparing the efficacy and tolerability of different TNF inhibitors are scarce, in particular the comparison between certolizumab pegol and golimumab.
Objectives: To compare the efficaciousness, drug survival and tolerability of certolizumab-pegol and golimumab in adult patients with establish arthritis (RA, JIA, SpA or unspecified polyarthritis) starting these treatments between February 2010 and December 2013 at out-patient unit at the Skåne University Hospital, Department of Rheumatology Lund/Malmö and two associated private rheumatology units.
Methods: All patients starting treatment with biologics were consecutively included in the South Swedish Arthritis Treatment Group (SSATG) register and regularly followed up according the standard protocol including: SJC/TJC, CRP, ESR, physicians global assessment of disease activity, patients' assessment of disease activity and pain (VAS global and VAS pain) and HAQ. Last follow up date was October 17th 2016. Kaplan-Meier survival analysis was used to estimate the drug survival. Possible predictors of drug survival were analysed using Cox regression model.
Results: In total, 352 patients (71% women, mean age 51 years, mean disease duration 12 years, started these treatments during study period. Of these, 168 received golimumab and 184 certulizumab-pegol. Mean treatment time was 31 months (range 0–77). Percentage of patients with RA, SpA, JIA and unspecified arthritis were 58,4%, 16,4%, 5,7%, and 19,5% respectively. Certolizumab-pegol was more used in RA (67% vs 49%) and JIA (8% vs 2%) while golimumab was more frequent among patients with SpA (21% and 12%) or PsA (23% and 10, respectively). Only 7% of golimumab and 10% of certulizumab-pegol patients received these drugs as first biologic treatment and approximately 50% of patients received these drugs as $\geq$3. biological treatment.
In golimumab treated patients mean DAS28 decreased from 4,3 (baseline) to 3,3 (3 months); 2,8 (6 months) and 2,7 (12 months) but levelled off at 36 months follow up. Corresponding mean DAS28 levels in certulizumab-pegol treated patients were 4,6 (baseline); 3,2 (3 months); 2,8 (6 months) and 2,6 (12 months). The similar pattern was seen in changes in HAQ and CDAI over the study time. There were no statistically significant differences in DAS, HAQ or CDAI between treatments at any follow up visit. At the end of follow up 64 (38%) of golimumab and 60 (32%) of certulizumab-pegol patients remained on their treatment. No significant difference in drug survival was seen between the treatments (Figure). Patients with spondylartropathy had significantly better survival on golimumab compared to RA patients (p=0,005)whicih remained after adjustment for age, gender, CRP, number of previous biologics and concomitnt methotrexate at baseline.



Conclusions: Spondylarthropathy including psoriatic arthritis was associated with better drug survival on golimunab compared to certolizumab pegol. No other significant differences in efficacy, tolerability or drug survival were seen between golimumab and certolizumab pegol in patients with established arthritis in daily clinical practice. Approximately one third of patients starting these treatments remained on treatment after 3 years.
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SAT0144 TUMOR NECROSIS FACTOR-ALPHA INHIBITORS AND PSYCHIATRIC SIDE EFFECTS: RESULTS FROM THE FRENCH PHARMACOVIGILANCE DATABASE

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Background: Although Tumor Necosis Factor alpha (TNF-α) is a major proinflammatory cytokine in the brain, potential psychiatric side effects of TNF-α inhibitors have been little investigated. Manic and psychotic disorders are not recognized as TNF-α inhibitors' side effects even though few reports of such complications have been reported.
Objectives: This study reports cases with psychiatric symptoms (in the spectrum of psychotic and manic disorders) that occur during treatment with tumor necrosis factor alpha (TNF-α) inhibitors and aims to evaluate the role of these agents as causative factors.
Methods: We searched the French Pharmocovigilance Database for consecutive cases of positive psychiatric side effects reported during treatment with TNF-α inhibitors. Major psychiatric symptoms were defined, according to DSM-V, as mania and psychosis, and minor psychiatric symptoms as psychomotor agitation, euphoria, hallucinations, personality distortion, and increased libido. Each case had one major symptom or at least one minor symptom.
Results: Among 7912 consecutive cases of side effects registered in the database for TNF-α inhibitors, 184 reported psychiatric symptoms, and of these, 71 met inclusion criteria, whereas 113 met an exclusion criterion. Depression was the most frequent cause for exclusion. TNF-α inhibitors were the only medication suspected in 56 cases (79%). The time between beginning TNF-α inhibitors and onset of symptoms varied from hours to months with a median time of 49 days (IQR=156); initial symptoms mostly worsened under treatment. TNF-α inhibitors were withdrawn in 42 (61%) cases. The improvement of symptoms was significantly associated with treatment withdrawal (78% versus 22%, *p=0.01*). Relapses occurred after rechallenge of TNF-α inhibitors in three of four patients.
Conclusions: We report the first cohort of 71 cases with psychiatric symptoms in the spectrum of manic and psychotic disorders during treatment with TNF-α inhibitors. Our experience suggests that anti-TNFα therapy may cause manic or psychotic side effects.
Disclosure of Interest: None declared