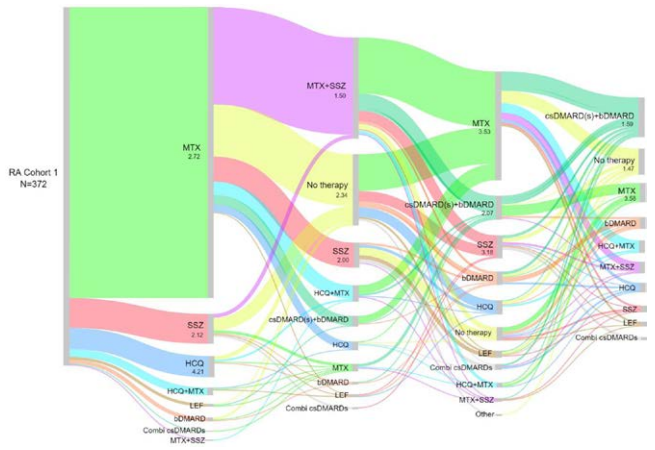

Figure 1. Sankey diagram of the treatment pathway of the first 3 switches of RA patients. The average duration of treatment of a flow is displayed in years if the flow included more than 20 patients. (MTX= methotrexate; SSZ= sulfasalazine; HCQ = hydroxychloroquine; LEF= leflunomide; bDMARD= monotherapy bDMARD; Combi csDMARDs= combination therapy of csDMARDS; csDMARD(s)+bDMARD= combination therapy of one or two csDMARD(s) + a bDMARD; No therapy= no treatment received >3 months; Other = medication that is not a (cs)(b)DMARD)

Conclusion: Sankey diagramming can be used to illustrate complex real-world treatment data of a treat to target cohort of RA patients. Treatment protocol adherence can be assessed with the help of a Sankey diagram. After 3 switches, the lower limit of adherence to the protocol was roughly 5%.

Disclosure of Interests: Tristan Coppes: None declared, Naomi Jessurun: None declared, Jurriaan Jansen: None declared, Kimberly Velthuis: None declared, Peter ten Klooster: None declared, Harald Vonkeman Consultant of: BMS, Celgene, Celltrion, Galapagos, Gilead, Janssen-Cilag, Lilly, Novartis, Pfizer, Sanofi-Genzyme, Grant/research support from: Abbvie

DOI: 10.1136/annrheumdis-2021-eular.2299

POS0621 DISEASE-SPECIFIC ADVERSE DRUG REACTION PROFILES OF ADALIMUMAB AND ETANERCEPT AS REPORTED BY IMMUNE-MEDIATED INFLAMMATORY DISEASE PATIENTS

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Background: Information on adverse drug reactions (ADRs) is generally clustered for all indications of a drug in the patient information leaflet. However, previous research has shown that participants of the Dutch Biologic Monitor (DBM) that use a biologic for their immune-mediated inflammatory disease (IMID) prefer to receive ADR information tailored to their own biologic an IMID (1). Currently, it is unclear whether the ADR profile of a specific biologic may differ between patients with different IMIDs, which would be vital information for health care providers (HCPs) in their patient guidance.

Objectives: To determine whether the profiles of ADRs attributed to adalimumab (ADA) and etanercept (ETN) reported by patients in the DBM differ between IMIDs.

Methods: The DBM is a prospective cohort event monitoring system for patient-reported ADRs attributed to biologics (2). Study data was extracted from the DBM for the period Jan 2017 – Oct 2020. ADRs were coded according to their corresponding Preferred Term (PT) following MedDRA terminology. Unique PTs were selected per participant and grouped under System Organ Classes (SOCs) (Figure 1) for ADA and ETN. SOCs contributing for <1% to the total number of reported ADRs were grouped as 'other'. Participants with more than one of the included IMIDs, i.e. Psoriatic Arthritis (PsA), Inflammatory Bowel Disease (IBD, i.e. Crohn's disease and ulcerative colitis), rheumatoid arthritis (RA), and axial spondyloarthritis (axSpA) including Ankylosing Spondylitis (AS), were excluded. Differences in ADR profiles between IMIDs were tested using the Fisher-Freeman-Halton's Exact Test with Monte Carlo simulation. SOCs of interest were separately tested with the Fisher-Freeman-Halton's Exact Test (no simulation) and subsequently corrected for multiple comparisons using the Benjamini-Hochberg (BH) correction.

Results: A total of 572 ADR reports from 218 participants using ADA and 450 ADR reports from 185 participants using ETN were analyzed (Table 1).

Overall, a statistically significant difference in patient-reported ADR profile between the assessed indications was found for ADA (p=0.011), but not for ETN (p=0.057). The following separate tests for selected SOCs of interest showed a significant difference in the frequencies of 'respiratory, thoracic and mediastinal disorders' and 'musculoskeletal and connective tissue disorders' between the different IMIDs for ADA after BH correction, but none for ETN.

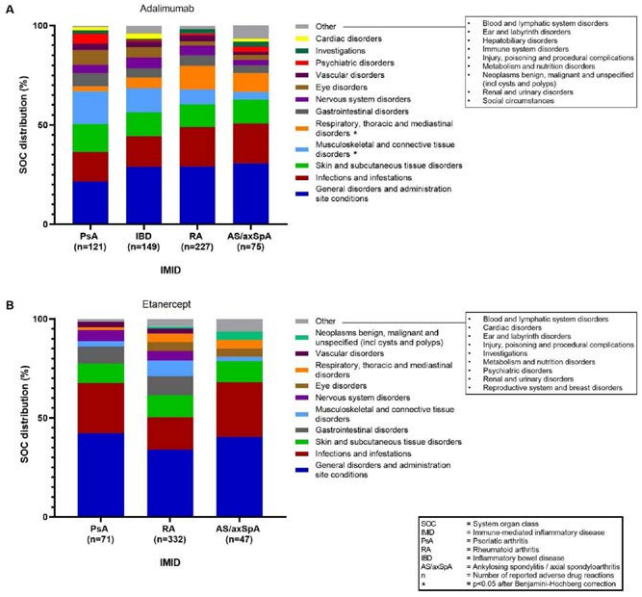

Figure 1. The disease-specific patient-reported ADR profile of ADA (A) and ETN (B) in IMID patients resulting from the Dutch Biologic Monitor

Table 1. Respondent characteristics.

Characteristics	ADA		ETN	
	n=218	%	*n*=185	%
Female gender, *n* (%)	140	64.2	129	69.7
Median age (IQR), years	56.0 (46.0-64.0)		58.0 (48.0-66.0)	
ADR reports	572	100.0	450	100.0
Indication for biologic therapy				
Rheumatoid arthritis	90	41.3	127	68.6
Psoriatic arthritis	46	21.1	35	18.9
Ankylosing spondylitis/axSpA	32	14.7	23	12.4
IBD[a]	50	22.9	0	0.0
Combination therapy[b]				
Methotrexate	63	30.3	70	40.2
Corticosteroids	25	12.0	21	12.1
Thiopurines	18	8.7	1	0.6
No combination therapy	87	41.8	59	33.9
Other	31	14.9	48	28.2

IQR: interquartile range; IBD: inflammatory bowel disease; axSpA: axial spondyloarthritis.[a]IBD includes Crohn's disease and ulcerative colitis.[b]The overall percentage exceeds 100% since patients can have a combination therapy consisting of one or more drugs.

Conclusion: Although only ADA shows a statistically significant difference in ADR profile between different IMIDs, more research with a larger sample size might show similar results for ETN. Furthermore, explanations for the differences found, such as disease-drug interactions, must be examined. This would help HCPs in providing disease-specific information and patient guidance.

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Disclosure of Interests: Lieke Roest: None declared, Leanne Kosse: None declared, Jette van Lint: None declared, Joep Scholl: None declared, Martijn van Doorn Grant/research support from: Leopharma, Novartis, Abbvie, BMS, Celgene, Lilly. Pfizer, Sanofi-Genzyme, Janssen Cilag, all outside the submitted work, Sander Tas Grant/research support from: AbbVie, Arthrogen, AstraZeneca, BMS, Celgene, Galapagos, GSK, MSD, Pfizer, Roche, Sanofi-Genzyme, all outside the submitted work, Michael Nurmohamed Speakers bureau: AbbVie, Bristol-Myers Squibb, Eli Lilly, Roche, Sanofi, all outside the submitted work, Consultant of: AbbVie, Celgene, Celltrion, Eli Lilly, Janssen, Sanofi, all outside the submitted work, Grant/research support from: AbbVie, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, MSD, Mundipharma, Novartis, Pfizer, Roche, Sanofi, all outside the submitted work, Harald Vonkeman Grant/research support from: AbbVie, Amgen, AstraZeneca, BMS, Celgene, Celltrion, Galapagos, Gilead, GSK, Janssen-Cilag, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi-Genzyme, all outside the submitted work, Renske Hebing: None declared, Phyllis Spuls Grant/research support from: departmental independent research grant for TREAT NL registry from different companies for the TREAT NL registry, is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of e.g. psoriasis and atopic dermatitis, for which financial compensation is paid to the department/hospital and, is Chief Investigator (CI) of the systemic and phototherapy atopic eczema registry (TREAT NL) for adults and children and one of the main investigators of the SECURE-AD registry, all outside the submitted work, Frank Hoentjen Speakers bureau: Abbvie, Janssen-Cilag, MSD, Takeda, Celltrion, Teva, Sandoz, Dr Falk, all outside the submitted work, Consultant of: Celgene, Janssen-Cilag, all outside the submitted work, Grant/research support from: Dr Falk, Janssen-Cilag, Abbvie, Takeda, all outside the submitted work, Eugène van Puijenbroek: None declared, Bart van den Bemt: None declared, Naomi Jessurun: None declared
DOI: 10.1136/annrheumdis-2021-eular.2300

POS0622 THE BLOOD T-CELL SUBSETS IN RHEUMATOID ARTHRITIS PATIENTS ON LONG-TERM IL-6 RECEPTOR BLOCKER THERAPY

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Background: Pleiotropic effects of IL-6 receptor antagonist tocilizumab (TCZ) in rheumatoid arthritis (RA) involve circulating T-cells. Preliminary reports have suggested that TCZ therapy can modulate T cell function and humoral immune responses in RA [1,2]. According to other studies, TCZ had no influence on T-lymphocyte subdifferentiation [3].
Objectives: To assess the effect of 12 months (m) TCZ therapy on T-cell phenotype, and to analyze the association between T-cell subsets and RA activity.
Methods: 36 active RA pts (29F/7M); median age 55[46; 64] years; disease duration 120[72; 1928]m; DAS28 score 6,3[5,7;6,7]; RF+100%, ACCP+ 86% were treated with TCZ (8 mg/kg every 4 weeks) in an open-label study. Immunophenotyping was performed at baseline, 6m and 12m. T-cell subpopulations and key laboratory parameters (CRP, RF, ACCP, MCV, MMP-3) were assessed.
Results: At baseline, the absolute counts of T cell subpopulations in RA pts - (CD3+), Th (CD3+CD4+), Tc (CD3+CD8+), NK cells (CD3-CD56+) - were comparable with counts in healthy donors (table1). At baseline, the absolute NK cells (CD3-CD56+) count correlated with MCV (r=0,35, p<0,05) and with MMP-3 (r=0,57, p<0,05) in RA pts. After 6m of TCZ therapy, 34% of pts were classified as good responders, 66% - as moderate responders; after 12m of TCZ therapy 68% of pts - as good responders, 32% - as moderate responders, according to the response criteria of the EULAR. Tc (CD3+CD8+) absolute count reductions were documented after 6m of TCZ therapy, absolute of T cells (CD3+) count and Th (CD3+CD4+) count - after 12m of TCZ therapy (table1). A positive correlation between Tc (CD3+CD8+) absolute counts and RF (r=0,50, p<0,05) was found after 6m of TCZ therapy. A negative correlation of Δ CRP was established with Δ T cells (CD3+) (r=-0,45], Δ Th (CD3+CD4+) (r=-0.47), and Δ Tc (CD3+CD8+) (r=-0,59, p<0,05 in all cases) after 12m of TCZ. The median absolute counts of T cells (CD3+), Th (CD3+CD4+) was lower than on healthy donors after 12m of TCZ therapy. NK cells (CD3-CD56+) counts and Th/Tc index did not change after 12 m of TCZ therapy vs healthy donors and baseline values.
Conclusion: Immunophenotyping in pts with active RA showed no difference in the absolute counts of T-cell subpopulations (T cells (CD3+), Th (CD3+CD4+), Tc (CD3+CD8+), NK cells (CD3-CD56+)) compared to healthy donors. T cells (CD3+), Th (CD3+CD4+) and Tc (CD3+CD8+) T cell counts dropped after 6 or 12m of TCZ therapy. Significant correlation between the T-cell subpopulations counts and values of RA laboratory indicators (CRP, MCV, RF, MMP-3) suggest potential T-lymphocytes involvement in RA pathogenesis.
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Table 1. Absolute counts of T-cell subpopulations at baseline, after 6 and 12 m of TCZ therapy

	Donors	Baseline	6m	12m
T cell (CD3+)	1,3 (1,2-1,8)^	1,2 (0,9; 1,7)*	1,1 (0,7; 1,4)	1,0 (0,7; 1,5)* ^
Th (CD3+CD4+)	0,9 (0,7-1,2) ^	0,8 (0,6; 1,0)*	0,7 (0,5; 1,0)	0,6 (0,4; 1,1) * ^
Tc (CD3+CD8+)	0,4 (0,3-0,5)	0,4 (0,2; 0,5)**	0,3 (0,2; 0,04)**	0,3 (0,3; 0,5)
Th/Tc	2,5 (1,9-3,1)	2,3 (1,4; 3,0)	2,3 (1,5; 3,6)	2,3 (1,4; 4,0)
NK (CD3-CD56+)	0,2 (0,2-0,5)	0,2 (0,1; 0,2)	0,2 (0,1; 0,3)	0,2 (0,1; 0,3)

Note: * - p<0,05 between pts at baseline and after 12 m of TCZ therapy; **- p= 0,02 between pts at baseline and after 6 m of TCZ therapy; ^ - p<0,05 between donors and pts after 12 m of TCZ therapy.

Disclosure of Interests: None declared
DOI: 10.1136/annrheumdis-2021-eular.2310

POS0623 CYTOKINE PRODUCTION BY BLOOD LYMPHOCYTES DEFINES A PROFILE ASSOCIATED WITH NON-REMISSION IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH TNF INHIBITORS

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Background: In clinical practice no more than 50% of the patients treated with TNF inhibitors (TNFi) achieve remission (REM). Previous investigations suggested that peripheral blood mononuclear cells (PBMC) may be markers associated with the TNFi treatment success[1].
Objectives: This study aims to analyse the intracellular cytokine production by PBMC and its association with REM achievement after 6 months (m) of TNFi treatment in patients with RA.
Methods: This was a prospective study including 62 patients with RA starting the 1st TNFi. PBMC were isolated from patients at baseline and after 6m of treatment with TNFi and cryopreserved until studied. In vitro stimulation and intracellular cytokine production by PBMC was performed as follow: in the presence of 2µg/mL brefeldin and 2µmol/L monensin monocytes were stimulated with 20ng/mL LPS during 4h whereas lymphocytes were stimulated with 50ng/mL phorbol 12-myristate 13-acetate and 750ng/mL ionomycin for 4h at 37ºC. To identify IL10-producing B cells, PBMC were pre-incubated with 3µg/mL of CpG oligonucleotide during 20h at 37°C prior to stimulation. Intracellular cytokine production (TNFα, IL6, GM-CSF, IL10) by the different cell subsets (monocytes, $CD4^+$ and $CD8^+$ T cells, naïve and memory B cells) was analysed by flow-cytometry. Clinical activity at baseline and after 6m was assessed by DAS28-ESR. REM was defined as DAS28≤2.6 at 6m. The association between cytokine production by each PBMC subset and REM was analysed through univariable and multivariable logistic regression models. Receiving operating curve (ROC) analysis was used to select the optimal ratio of cytokine production associated with REM status.
Results: After 6m of TNFi treatment, 30 (48%) patients achieved REM. No significant differences between REM and non-REM groups were observed for patients' characteristics at baseline except for DAS28, which was lower in the REM group (non-REM: 5.4±0.9; REM: 4.3±0.9; p<0.0001) (Table 1). Therefore, further analyses were adjusted by baseline DAS28. A lower ratio between calculated with the IL10 and TNFα production by B cells and by $CD4^+$ T cells (IL10 B/TNF CD4) at 6m was found for non-REM patients (non-REM: 0.31 vs REM: 0.54; p=0.007). Based on a ROC analysis, we found that a (IL10 B/TNF CD4)<0.54 at 6 m was