Rheumatoid arthritis - biological DMARDs

POS0636 PATIENT GROUPS IN RHEUMATOID ARTHRITIS IDENTIFIED BY DEEP LEARNING RESPOND DIFFERENTLY TO BIOLOGIC OR TARGETED SYNTHETIC DISEASE MODIFYING ANTIRHEUMATIC DRUGS

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Background: Cycling of biologic or targeted synthetic disease modifying antirheumatic drugs (b/tsDMARDs) in rheumatoid arthritis (RA) patients due to non-response is a problem preventing and delaying disease control.
Objectives: To assess and validate treatment response of b/tsDMARDs among RA patient groups identified by deep learning.
Methods: In the Swiss Clinical Quality Management of Rheumatic Diseases registry (SCQM), between 1998 and 2018, we identified all RA patients with a DAS28-erythrocyte sedimentation rate (esr) record within 6 months before start of the first b/tsDMARD. This first-time b/tsDMARD was the cohort entry at which patients were clustered through several runs of deep embedded clustering. Features, measured at cohort entry, included demographics, RA disease burden/duration, life-style factors, and other RA medication. To increase robustness of the obtained clusters, we grouped similar patient clusters together (further referred to as groups). Our outcomes were b/tsDMARD stop due to non-response, and separately a ≥20% reduction in DAS28-esr (RA disease activity in 28 joints using esr measures) as a proxy for treatment response. We followed all patients from cohort entry until b/tsDMARD stop or a maximum of 15 months follow-up. We assessed comparative effectiveness of b/tsDMARDs (ref. adalimumab) using Cox proportional hazard regression in each patient group by estimating hazard ratios (HR) with 95% confidence intervals (CI). We validated results obtained per patient group through stratified analyses according to most distinctive patient characteristics of the respective group, i.e. the characteristics that led to the respective grouping were also used to stratify the overall population by in this validation analysis.
Results: We obtained 24 clusters which comprised between 362 and 1481 patients (among 3516 unique patients). These clusters were grouped into 5 groups according to most distinct characteristics at b/tsDMARD initiation: 1) ≥2 csDMARDs and prednisone use, 2) male sex, 3) seronegativity, female sex, and no prednisone use, 4) rather low disease burden, 5) seropositivity, female sex, and a rather high disease burden/duration.
Comparative effectiveness results among validation strata confirmed comparative effectiveness results observed among the 5 groups: Patients with ≥2 csDMARDs and prednisone at b/tsDMARD initiation, men, as well as patients with a lower disease burden responded better to tocilizumab than to adalimumab (HRs of reaching ≥20% reduction in DAS28-esr: 5.46, 95% CI [1.76-16.94], HR 8.44 [3.43-20.74], and HR 3.64 [2.04-6.49], respectively). Furthermore, seronegative women without use of prednisone at b/tsDMARD initiation as well as seropositive women with a higher disease burden and longer disease duration had a higher risk of non-response with golimumab (HRs of b/tsDMARD discontinuation: 2.36 [1.03-5.40] and HR 5.27 [2.10-13.21], respectively) than with adalimumab.
Conclusion: Our results suggest that RA patient groups identified by deep learning may respond differently to individual first-line b/tsDMARDs. Thus, our results can possibly support the decision on the best choice of first-time b/tsDMARD for certain RA patients, which is a step forward towards personalizing treatment. However, further research in other cohorts is needed to verify our results.
Acknowledgements: We thank all patients and rheumatologists contributing to the SCQM registry, as well as the entire SCQM staff. A list of rheumatology offices and hospitals which contribute to the SCQM registry can be found at http://www.scqm.ch/institutions. A list of financial supporters of SCQM can be found at http://www.scqm.ch/sponsors. The professorship of Andrea M Burden is partially supported by PharmaSuisse and the ETH Foundation.
Disclosure of Interests: Maria Kalweit: None declared, Andrea Michelle Burden: None declared, Thomas Hügle Speakers bureau: Novartis, Janssen, Eli Lilly, Paid instructor for: Abbvie, Menarini, Consultant of: Janssen, Eli Lilly, Grant/research support from: Abbvie, Menarini, Pfizer, Theresa Burkard: None declared
DOI: 10.1136/annrheumdis-2022-eular.223

POS0637 SAFETY OF B/TSDMARDS FOR RA AS USED IN CLINICAL PRACTICE - RESULTS FROM THE LAST DECADE OF THE ARTIS PROGRAM

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Background: While the relative efficacy of treatments can be demonstrated in relatively small studies with limited follow-up, most safety concerns are infrequent, requiring longer follow-up and larger populations. This is recognized by the regulatory framework, where data from pivotal randomized controlled trials are usually considered sufficient for demonstrating efficacy and non-toxicity, but post-approval safety studies are required for many years to fully evaluate drug-associated risks. Though such regulatory safety-studies often focus on one drug (vs. all others), clinical decision-making requires data across all available treatment options. Long-standing longitudinal clinical registries, like the Anti-Rheumatic Therapies in Sweden (ARTIS) database, thus have a key role in assessing the relative safety of b/tsDMARDs, allowing simultaneous comparison of all drugs used in clinical practice, with consistent definitions of treatment cohorts, follow-up, and outcomes.
Objectives: To assess incidence rates of critical safety endpoints for individual b/tsDMARDs used to treat RA, updating previously published reports and including more recently introduced treatments.
Methods: Nationwide register-based cohort study including all RA patients in Sweden registered as starting any b/tsDMARD between Jan 1st 2010 and Dec 31st 2019, and followed until Dec 31st 2020. The incidence rates of selected outcomes, identified through national healthcare registers, were compared between individual b/tsDMARDs while adjusting for a range of potential confounders (covering demographics, RA-related characteristics and disease activity, and comorbidity) using Inverse Probability of Treatment Weighting. Probabilities were predicted by multinomial logistic regression, regressing all covariates on treatment status. Exposure time was counted from treatment start until stop (+90 days' lag time), censored at emigration and death.
Results: There were clear differences between patients starting individual b/tsDMARDs, in particular with TNF inhibitors more often used as a first line b/tsDMARD; sarilumab, baricitinib, and tofacitinib predominantly used later in the treatment course; rituximab used more often for older patients, and non-TNFi generally used more frequently for patients with higher disease activity or comorbidity. Expectedly, these differences translated into differences in the crude rate of safety endpoints. Several differences remained after confounder-adjustment (Table 1), including a higher rate of treatment discontinuation due to adverse events on baricitinib, tofacitinib, and sarilumab. Rituximab was associated with higher rates of several outcomes, but the confounder-adjustment markedly reduced risks and residual confounding likely explain part of the remaining increase. Baricitinib and tofacitinib were associated with higher rates of hospitalised herpes zoster, but not with similarly elevated rates of other serious infections. There were no clear differences in the rate of cardiovascular events or severe depression. Low number of events limit the comparison, in particular for sarilumab and tofacitinib.

Table 1. Weighted incidence rate per 1,000 person-years of selected safety outcomes.

DMARD	N	Discont. due to. adverse event	ACS	Stroke	Liver disease	Hosp. infection	Hosp. Herpes zoster	Hosp. depression	Any hosp.	All-cause mortality
ETA	8244	45	6.2	4.5	1.4	32	2.9	2.3	156	10.8
ADA	5069	46	5.9	5.6	1.1	36	3.5	1.5	166	9.5
INF	2832	50	8.2	5.8	3.1	43	3.2	2.0	197	12.7
CER	2072	54	6.4	7.0	2.5	34	3.6	1.7	172	11.0
GOL	1796	51	5.9	6.8	-	32	2.8	-	154	11.5
ABA	3254	56	7.3	4.7	1.9	36	2.3	1.6	172	13.9
RTX	3990	31	8.4	6.2	2.2	41	3.3	2.4	194	15.1
TCZ	2619	30	5.7	5.0	2.1	31	2.9	1.6	163	15.7
SAR	271	100	-	-	-	18	-	-	298	-
BARI	1665	69	3.0	4.2	1.4	37	8.8	2.6	173	16.7
TOFA	392	82	-	-	-	32	12.9	-	129	-

Note: Rates based on <5 events set to '-'.

Conclusion: We found large differences in the rate of treatment discontinuations due to adverse events across b/tsDMARDs, which were not generally mirrored by corresponding differences in the rates for specific serious adverse events.
REFERENCES: N/A
Acknowledgements: ARTIS has been or is currently supported by agreements with Abbvie, BMS, Eli Lilly, MSD, Pfizer, Roche, Samsung Bioepis, and Sanofi.
Disclosure of Interests: Thomas Frisell: None declared, Hannah Bower: None declared, Eva Baecklund: None declared, Daniela Di Giuseppe: None declared,

Bénédicte Delcoigne: None declared, Nils Feltelius Employee of: NF is employed by the Medical Products Agency (MPA), which is a governmental body. The views in this abstract may not represent the views of the MPA, Helena Forsblad-d'Elia: None declared, Elisabet Lindqvist: None declared, Ulf Lindström: None declared, Johan Askling Grant/research support from: Karolinska Institutet has entered into agreements with the following companies, with JA as PI: Abbvie, BMS, Eli Lilly, Galapagos, Janssen, Pfizer, Roche, Samsung Bioepis and Sanofi.
DOI: 10.1136/annrheumdis-2022-eular.341

POS0638 RECOMMENDATIONS FOR COST-EFFECTIVE USE OF BIOLOGICAL AND TARGETED SYNTHETIC DMARDS IN INFLAMMATORY ARTHRITIS: RESULTS FROM AN INTERNATIONAL DELPHI STUDY

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Background: Biological and targeted synthetic disease modifying antirheumatic drugs (b/tsDMARDs) are effective treatments for rheumatoid arthritis (RA), psoriatic arthritis (PsA) and spondyloarthritis (SpA), but associated with high costs. Therefore, various strategies for safe and cost-effective use of these drugs have been developed, such as tapering and biosimilar use. However, overarching recommendations on how clinicians or hospitals can use these strategies in clinical practice are absent.
Objectives: To develop evidence-based multidisciplinary recommendations on strategies for cost-effective use of b/tsDMARDs in the treatment of RA, PsA and SpA.
Methods: A task force was formed consisting of 13 experts in rheumatology, epidemiology and/or pharmacology from seven European countries. Relevant strategies for cost-effective use were collected and defined using one-to-one interviews with each task force member followed by group discussion. Next, a scoping review in PubMed and Embase was performed to summarize the evidence on each strategy, followed by a Delphi procedure and five online meetings, to form a set of overarching principles and recommendations. Levels of evidence and strengths of recommendations were determined in accordance with the 2018 EULAR additional guidance.[1] If consensus was reached on the formulation of the recommendation in the group meeting, voting on level of agreement was performed by every task force member separately using an online form. Level of agreement varied from 0 (completely disagree) to 10 (completely agree).
Results: Twelve strategies for cost-effective use of b/tsDMARDs were identified and four overarching principles were formulated (Table 1). For 10 strategies, there was enough evidence available to form one or multiple recommendation(s). In total, 20 recommendations were formulated, focussing on: the use of loading doses (2); the use of biosimilars where available (2); combining a csDMARD with a b/tsDMARD to maximise efficacy (3); the use of disease activity guided dose optimisation (4); the use of a drug formulary policy in clinical practice (1); considering using a lower dose where approved (2); improving medication adherence (1); non-medical drug switching within or between drug classes (1); therapeutic drug monitoring and other predictors for selecting or tapering a b/tsDMARD (2); and the use of different routes of administration of the same b/tsDMARD (2). The level of agreement for the recommendations varied between 7.9 (SD 1.2) and 9.8 (0.4).

Table 1. Overview of strategies (A) and overarching principles (B) for cost-effective use of b/tsDMARDs in RA, PsA and SpA

A.Strategies	
Avoid dose loading	Biosimilar/generic drug use
Combination therapy	Disease activity guided dose optimisation
Drug formulary policy	Drug wastage
Initial lower dose	Medication adherence
Nonmedical drug switching	Optimizing pharmacokinetic exposure
Response prediction	Route of administration
B.Overarching principles	
Cost-effectiveness considerations are an important aspect of treatment, and rheumatologists should have a leading role regarding this.	
Treat-to-target is the cornerstone of b/tsDMARD based treatment in RA, PsA and axSpA.	
Treatment choices must be based on shared decision making between the patient and the rheumatologist.	
Reimbursement policies should cover cost-effective use of pharmacological treatments, both on- and off-label, when they are evidence based and supported by (inter)national guidelines.	

Conclusion: These evidence-based recommendations provide caregivers in rheumatology with a consensus on strategies for cost-effective use of b/tsDMARDs in RA, PsA and SpA. Because high-quality evidence was limited, we were not able to formulate recommendations on all strategies.
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[1] Additional guidance on the methodology for the development/update of EULAR recommendations, van der Heijde, D; de Thurah, A; June 2018.
Disclosure of Interests: Celeste van der Togt: None declared, Bart van den Bemt Speakers bureau: UCB, Pfizer, Sanofi-Aventis, Galapagos, Amgen en Eli Lilly, Daniel Aletaha Speakers bureau: Abbvie, Amgen, Lilly, Janssen, Merck, Novartis, Pfizer, Roche, Sandoz, Consultant of: Abbvie, Amgen, Lilly, Janssen, Merck, Novartis, Pfizer, Roche, Sandoz, Grant/research support from: Abbvie, Amgen, Lilly, Novartis, Roche, SoBi, Sanofi, Rieke Alten Speakers bureau: Abbvie, BMS, Celltrion, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, Roche, Paid instructor for: Abbvie, BMS, Celltrion, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, Roche, Consultant of: Abbvie, BMS, Celltrion, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, Roche, Grant/research support from: Abbvie, BMS, Celltrion, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, Roche, Katerina Chatzidionysiou Consultant of: Eli Lilly, AbbVie, Pfizer, James Galloway: None declared, John Isaacs Speakers bureau: AbbVie, Gilead, Roche, UCB, Grant/research support from: GSK, Janssen, Pfizer, Denis Mulleman Speakers bureau: GSK, Chugai Pharma France, Patrick Verschueren Speakers bureau: Eli Lilly, MSD, Galapagos, Roularta, Consultant of: Galapagos, Gilead, Pfizer, Sidekick Health, Eli Lilly, Nordic Pharma, Abbvie, Celltrion, BMS, UCB, Grant/research support from: Holder of the Pfizer Chair Management of Early Rheumatoid Arthritis at KU Leuven, Arnold Vulto Speakers bureau: Amgen Inc; Biogen Idec Ltd; Bristol Meyers Squibb; Effik Benelux, F. Hoffmann-La Roche Ltd; Eli Lilly; Febelgen/Medaxes; Medicines for Europe AISBL; Mundipharma; Pfizer/Hospira, and Hexal / Sandoz Ltd., Paid instructor for: Effik Benelux, Fresenius/Kabi, Amgen, Sandoz/Novartis, Consultant of: Biogen Idec Ltd; Effik Benelux, Fresenius/Kabi, Pfizer / Hospira Inc; Sandoz/Novartis Ltd.; Samsung Bioepis., Paco Welsing: None declared, L.M. Verhoef: None declared, Alfons den Broeder Grant/research support from: Abbvie, Galapagos, Pfizer, Novartis, Lilly, Sanofi, Gilead
DOI: 10.1136/annrheumdis-2022-eular.433

POS0639 PHARMACOKINETIC BOOSTING TO ENABLE A ONCE-DAILY REDUCED DOSE OF TOFACITINIB IN PATIENTS WITH RHEUMATOID ARTHRITIS AND PSORIATIC ARTHRITIS

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Background: Tofacitinib is an effective drug for rheumatoid arthritis (RA) and psoriatic arthritis (PsA). As tofacitinib is metabolized by the CYP3A4-enzyme, the manufacturer recommends to reduce the dose with 50% when combined with CYP3A4-inhibitors. This creates an opportunity to improve cost-effectiveness and patient experience by deliberately combining tofacitinib 5 mg once daily with a registered CYP3A4-inhibitor, cobicistat.
Objectives: Primary: pharmacokinetic (PK) bioequivalence of tofacitinib 5 mg and cobicistat 150 mg once daily (intervention) to tofacitinib 5 mg twice daily (control). Secondary: clinical efficacy (DAS28-CRP), safety, patient preference, and predictive modelling of long-term DAS28 and ACR20 response.
Methods: This open-label, cross-over, monocentre study (Sint Maartenskliniek, The Netherlands) included patients with RA or PsA, using tofacitinib 5mg twice daily for ≥ 14 days without co-medication affected by CYP3A4-inhibition. At the first sampling day, plasma samples of tofacitinib were collected pre-dose and 0.5, 1, 2, 3, 4, 6, 9 and 12 hours post-dose. Subsequently, patients switched treatment to tofacitinib 5 mg and cobicistat 150 mg once daily, and 2-6 weeks thereafter, another PK sampling was performed at the same timepoints and additionally at 24 hours post-dose. PK bioequivalence was defined as the 90% confidence interval of the average tofacitinib concentration ($C_{avg,ss}$) geometric mean ratio (GMR) falling between 80-125%. Secondary endpoints included efficacy (change in mean DAS28-CRP between sampling days), safety, and patient preference (7-point Likert scale at study end). Additionally, differences between both regimens in DAS28 and probability of ACR20 response were predicted using a validated PK/PD model.[1]
Results: Between September 2019 and March 2021, 27 participants were included. Twenty-five participants completed both PK measurements and were included in the primary analysis. The $C_{avg,ss}$ GMR was 84.8%, 90% CI 75.1% to 95.6%. The difference in absolute DAS28-CRP was 0.05 (95% CI -0.50 to 0.59, intervention to control). There were no significant or relevant