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Rheumatoid arthritis - non biologic treatment

THU0168 PATIENTS' POSITIVE BELIEFS AND CERTAINTY PREDICT METHOTREXATE ADHERENCE IN A RHEUMATOID ARTHRITIS COHORT: THE RAMS STUDY

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Background: Living with RA confers substantial uncertainty about the long-term outcomes of the disease and the occurrence of possible medication associated adverse events (ADEs). This latter uncertainty may be particularly apparent when new therapies are initiated and reduce patient adherence.
Objectives: The aim of this study was to evaluate whether patients' negative and/or uncertain illness beliefs during methotrexate (MTX) therapy are associated with adherence.
Methods: This was a sequential mixed-methods design study using data from the Rheumatoid Arthritis Medications Study (RAMS). RAMS is a 12 month observational study in the UK recruiting patients with RA commencing MTX for the first time. Clinical and demographic data were collected at baseline and patients were asked to complete a weekly diary recording MTX intake (adherence) and reasons for not taking MTX. In addition there was a free text section in the diary where patients could comment about any aspect of their disease or care. Six month diary data were used for the purpose of this study.Patients were categorised as non-adherent if the proportion of adherent weeks was <90%.
Phase 1:Using a random sample (n=50/417) of patient diaries with free text comments a coding system was developed to categorise illness events and beliefs contained in these data. Inter-rater reliabilities for codes rated by three judges were calculated using intraclass correlation coefficients (ICC) and unreliable codes (ICC<0.6) dropped.
Phase 2:179 of 200 diaries from adherent and non-adherent individuals were randomly selected, coded and categorised into illness belief profiles (IBPs) by three researchers blind to adherence data.Univariate logistic regression analyses adjusted for age and gender were used to investigate the association between IBPs and MTX non-adherence behaviour (<90% adherence).
Results: Phase 1: ten codes with ICCs ranging from 0.6–1.0 were used to create three IBPs (Table):"Positive & Certain" (PC), "Negative & Certain" (NC) and "Negative and Uncertain" (NU) (Fig.).
Phase II, the median age of the sample was 62 [51.8–65.6] years, 67% were women and the median disease activity score was 4.3 [3.4–5.2]. Being PC lowered the odds of non-adherence (OR 0.32, 95% CI 0.12–0.85), being NU increased the odds of non-adherence (OR 2.7, 95% CI 1.0–7.0), but being NC didn't associate with non-adherence during the first six months of therapy (OR 0.98, 95% CI 0.31–3.2).

Table 1. The reliability (ICC) of codes that contribute to the IBPs

IBP	Codes	ICC (95% CI)
Positive	Treatment response	0.73 (0.60–0.83)
	ADE cessation	0.79 (0.68–0.87)
	Positive emotion	0.77 (0.65–0.85)
	Positive attribution	0.60 (0.44–0.74)
Negative	Disease flare	0.93 (0.89–0.96)
	ADE	0.81 (0.71–0.88)
	Severity attribution	0.62 (0.46–0.75)
	Negative emotion	0.81 (0.71–0.89)
	Negative attribution	0.81 (0.71–0.88)
Certainty/Uncertainty	Certainty/Uncertainty	1.0 (1.0–1.0)

Positive & Certain (N=89)	Negative & Certain (n=148)	Negative & Uncertain (n=35)
"Pain has reduced in my joints this week"	"Methotrexate too strong, however in lot of pain in knees"	"I think the cramp may be the HCQ not the MTX"
"Can write with right hand"	"Pain is still unbearable and (MTX) not working"	"It may be the flu injection what has give me side effect"\
"Wrists much less painful"	"Ankle and wrist still painful and inflamed"	"Fingers and wrist quite painful & lots of pins and needles. Due to heat?"
"Not feeling any side effects"	"Methotrexate had no effect at all at this stage"	"Upset stomach, ate out, so could have been that?"
"Feeling better this week"	"Same as last week seems to be worse"	"Swelling of wrist-knee don't know if tabs caused it"
"Almost all pain gone - whoopee!"	"Stomach ache and nausea much worse after every meal"	"Difficult to tell if MTX side effects, still ill"

Figure. Examples of patient comments that contributed to each IBP

Conclusions: People who are uncertain about how to attribute illness events are less likely to adhere within the first six months of starting MTX therapy. Encouraging patients to actively monitor their progress with therapy and providing them with support to understand likely effects of MTX may help optimise DMARD use.
Disclosure of Interest: None declared
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THU0169 ONE-THIRD OF PATIENTS WITH RHEUMATOID ARTHRITIS ELIGIBLE FOR A FIRST BIOLOGIC ARE NOT ADHERENT TO METHOTREXATE: RESULTS OF FORGET, A CROSS-SECTIONAL SURVEY OF 244 PATIENTS

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Background: Adherence to Methotrexate (MTX) is not optimal in patients with rheumatoid arthritis (RA)[1]. Low adherence may lead to insufficient response and unjustified initiation of biologics.
Objectives: The objectives were 1-assess the self-reported adherence rate to MTX of RA patients insufficient responders to MTX (MTX-IR) when an initiation of biologics was being considered 2- Investigate the factors of low adherence among these patients 3- collect the physicians' estimation of their patients' adherence level.
Methods: Patient recruitment was done through rheumatologists: RA patients, MTX-IR, biologic-naive, eligible for a biologic according to the rheumatologist's opinion. The rheumatologist completed a questionnaire on his practice and estimation on the patient's level of adherence and provided the patient with a self-administered questionnaire on his disease and treatments, to be sent directly to the data center. The patient's questionnaire contained the CQR19 (Compliance Questionnaire for Rheumatology [2]. The purpose of assessing adherence was not specified to the patient.
Results: From May to July 2016, 78 rheumatologists recruited 269 patients who referred 244 self-administered questionnaires, 214 assessed for CQR 19 score; 200 questionnaires were completed by both patients and their rheumatologist. Patients were 72% women, mean age 54 years, 58% had at least 1 comorbidity, mean DAS28 score 4.07, mean RAID score 5.7/10. The percentage of non-adherent patients was 34%: adherence rate <80% according to the CQR.
Non-adherent patients had a higher RAID score (5.7 vs 5.0; p<0.01) whereas DAS 28 was not significantly different (4.14 vs 4.04). They more often presented osteoporosis (18% vs 4%, p<0.01), reported reluctance to take treatment (40% vs 24%, p<0.01), had more negative beliefs (40% vs 24%; p<0.01), and poor support from relatives (67% vs 84%, p<0.011). Good-adherent patients were more often followed in a private practice (31% vs 10%, p<0.01) and reported more information received from their rheumatologist (94% vs 85%, p<0.05). No correlation was found between adherence and age, subcutaneous versus oral route of administration or perceived tolerance.
88% of rheumatologists reported they detect adherence at every consultation, asking direct (76%) or open (46%) questions. Adherence was underestimated by rheumatologists: a 67% concordance was found between the rheumatologist's rating and the patient's reported adherence. Non-adherent patients to MTX were more often proposed biologic treatment in combination with MTX than patients with good compliance (91% vs 68%, p<0.01).
Conclusions: This survey showed for the first time that 34% of MTX-IR patients show poor adherence to MTX at the time of the initiation of a first biologic. Negative beliefs and poor support from relatives are factors of non-adherence. Studies will be needed to understand physicians' attitudes toward non-adherence and what strategy of biologics prescription they are likely to consider.
References:
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THU0170 OUTCOMES OF THE RAPID DOSE ESCALATION OF METHOTREXATE IN JAPANESE PATIENTS WITH EARLY RHEUMATOID ARTHRITIS; RESULTS FROM A RANDOMIZED CONTROLLED TRIAL

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Background: Methotrexate (MTX) is the anchor drug for treatment of rheumatoid arthritis (RA), but tolerance to MTX is substantially different across ethnics and few studies have assessed efficacy and safety of rapid dose escalation regimen of MTX in Japanese patients with early RA.

Objectives: To evaluate outcomes of rapid dose escalation regimen of MTX compared with conventional treatment.
Methods: We implemented a randomized, controlled trial that enrolled patients with RA who fulfilled all of the following criteria: 20 to 70 years-old, disease duration ≤2 years, SDAI ≥11, and without prior use of MTX, tacrolimus (TAC) or biologics. Patients were randomized into rapid escalation (RE) group or conventional treatment (CT) group at 1:1 ratio. In RE group, doses of MTX were escalated up to 0.25 mg/kg/wk within 8 wks after start of MTX and increased maximum tolerable dose or 16 mg/wk until wk 12. If a patient achieved SDAI remission at wk 12, MTX was continued at the same dose. If a patient did not achieve SDAI remission at wk 12 or showed intolerance to MTX, use of TAC or TNF inhibitor (TNFi) were allowed. In CT group, patients were treated with either MTX, TAC, salazosulfapyridine, or bucillamine by the discretion of physicians until wk 12. If a patient achieved SDAI remission at wk 12, same treatment was continued. If a patient did not achieve remission at wk 12, use of TNFi was allowed. Patients were treated by the discretion of physicians at wk 24 and onward. We set two primary endpoints; the percentage of patients achieving SDAI remission and Boolean remission at wk 24. We planned to enroll 120 patients per arm based on expected SDAI remission rates at wk 24, alpha and beta errors and dropout rates.
Results: Enrollment was terminated prematurely and all patients were followed for 48 wks. Of 115 enrolled patients, 57 were randomly assigned to RE group and 58 to CT group. Baseline demographics were similar between the two groups. The median baseline values (RE vs. CT) were 24.9 and 25.9 for SDAI, 0.88 and 0.69 for HAQ, and 0.64 and 0.61 for EQ-5D, respectively. At wk 24, the percentages of patients achieving remission in RE and CT groups were 42% and 28% by SDAI criteria (p=0.1, χ^2 test), and 35% and 17% (p=0.03, χ^2 test) by Boolean criteria, respectively. Median values of HAQ at wk 24 in RE and CT groups were 0 and 0.13 (p=0.096, M-W U test), and those of EQ-5D were 0.78 and 0.77 (p=0.12, M-W U test), respectively. At wk 48, these values were not statistically different between the two groups. There were no significant differences between the two groups with incidence of severe adverse events.
Conclusions: The rapid dose escalation regimen of MTX provided significantly superior Boolean remission rate and tended to provide superior SDAI remission than conventional treatment in patients with early RA in the short term.
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THU0171 INCREASED FUNCTIONAL ACTIVITY OF FOXP3+REGULATORY T CELLS IN THE PERIPHERAL BLOOD OF DMARDS-NAÏVE METHOTREXATE-TREATED PATIENTS WITH EARLY RA USING

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Objectives: To analyze the effect of methotrexate (MT) therapy on the percentage and absolute number of FoxP3+ regulatory T (Treg) cells in the peripheral blood of MT-naïve patients (pts) with early RA we used Treg immunostainingwith antibodies to surface markers and Foxp3 with subsequent flow cytometric analysis
Methods: 45 MT-naïve pts with early RA (39 females, Me;IQR age 52.0 (32.5–57.5) years, RA duration 5 (4–6) months, DAS 28 5.01 (4.18–5.8), RF positive -71.1%, ACPA - positive-88.9%) were included into the study. All pts were administered subcutaneous MT as the first-line DMARD at 10 mg/week with rapid dose escalation up to 20–25 mg/week. Human blood mononuclear cells were isolated from whole venous blood by Ficoll–Hypaque centrifugation and subjected to multicolor flow cytometry analysis. Tregs were stained for different surface markers, and proportions of marker-positive subsets (FoxP3+CD25+; CD152+surface; CD152+intracellular; FoxP3+CD127-; CD25+CD127-; FoxP3+ICOS+; FoxP3+CD154+; FoxP3+CD274+) were determined; 20 healthy donors made the control group
Results: After 24 weeks of MT therapy value DAS 28 was 3.1 (2.7–3.62); SDAI 7.4 (4.2–11.4); DAS 28 remission/low disease activity was achieved in 22 (56.4%) pts, based on SDAI – in 25 (64.1%) pts; while MT failure based on EULAR response was documented in 4 (10.3%) pts. Lower percentages of FoxP3+CD25+ cells ((5.53 (4.09–6.48 vs 6.92 (5.84–7.96)), percentages and absolute number of FoxP3+ICOS+ cells ((6.91 (2.14–11.47) vs 10.83 (9.27–13.7); 0.0035 (0.0013–0.0067) vs 0.0068 (0.0039–0.009)), and percentages and absolute number of FoxP3+CD154+ cells ((0.47 (0.19–0.83) vs 1.51 (1.12–2.08); 0.0002 (0.00009–0.0005) vs 0.00087 (0.00047–0.0014)), and FoxP3+CD274+ T-cells (0.63 (0.34–1.49) vs 1.94 (1.16–2.25); 0.0003 (0.0002–0.00065) vs 0.001 (0.0006–0.0016), $p<0,05$ in all cases) were documented in early RA pts versus healthy donors.
An increase in the percentage of CD4+cells (from 45.0 (38.0–49.2) to 46.8 (39.9–53.2)); an increase in the relative and absolute number of CD152+surface 0.65 (0.22–1.67) vs 2.07 (1.11–3.81); 0.0002 (0.0001–0.0008) vs 0.0007 (0.0004–0.002); and moderate decrease in the relative and absolute number of FoxP3+ICOS+ cells 5.3 (2.1–11.3) vs 4.1 (1.6–6.6); 0.002 (0.001–0.006) vs 0.0015 (0.0006–0.003), $p<0.05$ in all cases, was registered after 24 weeks of MT therapy. After 24 weeks of MT therapy the level of CD152+surface in the RA pts group was higher compared with healthy donors 2.1 (1.11–3.81) and 0.51 (0.34–1.2); 0.0007 (0.0004–0.002) and 0.0003 (0.00014–0.0008), respectively, $p<0.05$
Treg levels and phenotype were analyzed in pts groups based on MT efficacy by 24th week of treatment. Higher percentages and absolute number of FoxP3+CD274+ cells (1.25 (0.43–2.3) 0.0004 (0.0002–0.001) were detected in patients achieving SDAI remission (n=25), compared to pts with moderate disease activity (SDAI>11 n=14) (0.44 (0.2–0.69) 0.00016 (0.0001–0.0004), $p<0.05$)
Conclusions: MT therapy in early RA pts results in increased Treg suppressor activity according to growing percentages and absolute number of CD152+surface and FoxP3+CD274+ cells, more pronounced among pts, achieving remission/low disease activity following treatment. Increased levels of these markers are indicative of improved Tregs functional activity after successful MT therapy
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THU0172 IMPROVEMENT OF DISEASE ACTIVITY IN A 5-YEAR COHORT OF RHEUMATOID ARTHRITIS PATIENTS TREATED UNDER TREAT TO TARGET RECOMMENDATIONS AND A MULTISPECIALITY CARE MODEL RECEIVING CONVENTIONAL DMARD THERAPY

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Background: Treat to Target (T2T) strategy becomes from the need to develop therapeutic targets and tools to achieve defined outcomes in rheumatoid arthritis (RA), this strategy has become recognized as a standard of good practice embodying the principle that rapid attainment of remission, or low disease activity, can halt joint damage and maintain good quality of life.
Objectives: The aim of this study was to describe global change in Disease Activity Score 28 (DAS28) using T2T strategy for a 5 year period in patients with conventional DMARD therapy in a large cohort of patients from a Colombian specialized in RA center with multidisciplinary care model (MCM).
Methods: A descriptive dynamic cohort study was performed. Records of patients using conventional DMARD treatment from specialized in RA center were reviewed; those patients were followed-up under T2T standards. Clinical follow-up was according to DAS28 as follows: every 3–5 weeks (DAS28 >5.1), every 7–9 weeks (DAS28 ≥3.1 and ≤5.1), and every 11–13 weeks (DAS28 <3.1). Therapy had to be adjusted with DAS28 >3.2 unless patient's conditions don't permit it. MCM model means that every patient is seen by the other specialties involved in care as a minimum three times a year. We divided patients in three groups: low disease activity (LDA), moderate disease activity (MDA) and severe disease activity (SDA) patients. Descriptive epidemiology was done, percentages and averages were calculated; the median of each variable was analyzed using t-Student assuming normality for DAS28 distribution and the level activity disease was analyzed using Pearson's statistics.
Results: We included 1443 patients, 84% were women and 16% were men. Mean age was 62±11 years; mean DAS28 at beginning was 4.0±1; regarding disease activity 57% were in moderate disease activity and 17% in severe disease activity. While at 5 year follow up mean DAS was 2.92±0.65, 48% achieved remission, 30% low disease activity, with decrease to 20% in moderate disease activity and 2% in severe disease activity.

ACTIVITY LEVEL	TIME 0 n(%)	2012-2013 n(%)	2013-2014 n (%)	2014-2016 n (%)
REM	-	380(26%)	530(37%)	698(48%)
LDA	380 (26%)	495(34%)	487(34%)	437(30%)
MDA	782 (54%)	439(30%)	401(28%)	284(20%)
SDA	281 (19%)	129(9%)	25(2%)	24 (2%)

Conclusions: There is a significant improvement of DAS28 in a cohort of RA