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FM 1

Predictors of infection in patients treated with rituximab for autoimmune diseases

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Introduction: Rituximab (RTX) has emerged as a promising therapeutic alternative for patients with rheumatoid arthritis (RA) and a variety of other autoimmune diseases (AID). The risk of severe infection in these patients varies upon the different studies and several risk factors have been identified. In this study, we investigated infection rates and predictors of infection in our patients treated with RTX.
Methods: We conducted a retrospective study of 161 patients treated with RTX for RA and other AID in the University Hospitals of Geneva.
Results: The incidence rate of severe infection was 24.9/100 patient-years in AID patients and 5.9 in RA patients (p <0.001). Low B-Ly counts at the time of first or subsequent RTX infusion were not associated with an increased risk of subsequent severe infection (adj HR 0.55, p = 0.60) or any infection (adj HR 0.85, p = 0.58). Patients with B cell lymphopenia at any time during follow-up did not present significantly more severe infections than patients without. Significant predictors of severe infection were a diagnosis other than RA (adj HR 4.68, p <0.001), hypogammaglobulinemia <7 gr/L (adj HR 2.36, p = 0.01), age (adj HR 1.03, p = 0.01), and diabetes (adj HR 3.61, p = 0.01). Significant predictors of any infection were diagnosis other than RA (adj HR 3.46, p <0.001), age (adj HR 1.02, p = 0.005), chronic disease (adj HR 4.19, p = 0.007), and diabetes (adj HR 5.51, p = 0.012).
Conclusions: In this population treated with RTX for RA and other AID, we confirmed the higher risk of severe infection conferred by low IgG levels, older age, diabetes, and AID other than RA. B-Ly counts before RTX infusion were not predictive of severe -or of any- infections. High rates of infection in non-RA patients were observed.

FM 2

Neutrophil extracellular trap formation measured by nucleosome capture ELISA in serum is highly specific and sensitive for rheumatoid arthritis diagnosis

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Introduction: Current diagnostic tests such as RF or ACPA detection have limited use, as they show low specificity or are restricted only to a sub-group of RA patients. Neutrophil extracellular trap (NET) generation, the extrusion of cellular chromosomal material, has been reported mainly as a response to infectious agents, but has also been linked to the pathogenesis of autoinflammatroy processes in preeclampsia, systemic lupus erythematosus, and, recently, rheumatoid arthritis (RA) [1, 2]. We have previously observed that serum samples from patients had significantly higher cell-free DNA levels than those of comparable controls [3]. The aim of our study was to identify surrogate markers of NET formation in the serum and to evaluate their potential in differentiating rheumatoid arthritis cases fom healthy controls.
Methods: Serum from healthy controls and cases with RA fulfilling the ACR 1987 criteria was analysed for cell free DNA by quantitative PCR for GAPDH. Neutrophil elastase (NE), myeloperoxidase (MPO), MPO/DNA complexes and nucleosomes were determined by ELISA. Healthy control and RA groups were compared by the Mann-Whitney t-test. Receiver operator characteristic (ROC) curves were calculated with the standard errors.
Results: Although cf-DNA levels were also significantly elevated in cases with RA, cell-free DNA/nucleosome elevations attained a far higher degree of significance. With an ROC area under the curve of >97% the sensitivity and specificity for distinguishing between RA cases and healthy controls were 91% and 92% at a cut-off of 0.78. The values achieved by NE, MPO and MPO/DNA complexes were far inferior.
Conclusions: The detection of nucleosomes in the serum of RA cases can be utilized to discriminate between healthy contrla and cases with RA wiht remarkable sensitivity and specificity. This also applied to ACPA negative RA cases. The nucleosome assay may be further enhanced by incorporating modified components, such as citrullinated H3, in the assay.

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FM 3

Ultrasound Doppler activity correlates with systemic autoimmunity and swollen joints in a healthy population at risk for rheumatoid arthritis

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Introduction: Diagnosing rheumatoid arthritis (RA) early and identifying pre-clinical RA has become a high-stakes undertaking. In RA patients, musculoskeletal ultrasound (US) is more sensitive than clinical assessment for synovitis detection and US abnormalities were associated with arthritis development in auto-antibody positive arthralgia patients. Doppler activity has been correlated with erosion progression and short term relapse. Whether US is associated with joint involvement in healthy individuals at increased risk for RA is unknown. The aim of this study was to assess the value of US to detect specific phases leading to the development of RA in a healthy population at increased risk of RA.
Methods: This study is nested within an ongoing prospective cohort study of healthy first-degree relatives of RA patients (FDRs), who had no established rheumatic disease at inclusion. Data collection included health questionnaires, physical examination and blood tests, including inflammatory markers, HLA-DR genotyping, rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP2) levels by ELISA. A standardized US examination was performed according to the OMERACT criteria: synovitis was scored in B-mode and Doppler by a semi-quantitative scale ranging from 0 to 3 on MCPs and PIPs 2 to 5, wrists, olecranon fossa and knees. To test if US was independently associated with the presence of systemic autoimmunity associated with RA (anti-CCP, RF), we used logistic regression, adjusting for potential confounders such as age, BMI, Caucasian race, smoking and shared epitope.
Results: 114 consecutive healthy FDRs were included. Baseline characteristics were similar between subjects with anti-CCP2 antibodies (group 1) and without (control). Doppler activity was detected more often in group 1 compared to control 60% vs 36% (p = 0.02, adjusted OR 8.34 [95%CI: 1.39–50.03]). The mean Doppler score was also significantly higher in group 1 (1.5 vs 0.69, p = 0.03, adjusted OR: 1.8 (95%CI: 1.07–3.12)). Doppler was not associated with RF, but only with anti-CCP2. Doppler was also associated with the presence of synovitis on physical examination (OR 1.07 (95% CI: 1.01–2.89). Neither the presence of synovitis grade 2 or 3 on B-mode (30% vs 41%, p = 0.55) nor the mean B-mode score (7.4 vs 6.6, p = 0.5) allowed to discriminate the 2 groups.
Conclusion: This is the first study to assess US in healthy first-degree relatives of RA patients. Doppler signal was associated with the presence of anti-CCP but not with RF. Doppler may indentify early signs of arthritis in a population at risk to develop RA.

P 1

Multidimensional associative factors for improvement in pain, function, and working capacity after rehabilitation of whiplash associated disorder

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Introduction: Whiplash associated disorder (WAD) and chronic neck pain after car accidents are multi-component phenomena associated with injury, physical dysfunction and maladaptive coping behavior. Chronic cases lead to high cost for individual and public health. This study aimed to determine short- and mid-term associative factors of neck pain relief, improved physical functioning, and improved working capacity (dependent variables) in patients suffering from WAD after a standardized, inpatient pain management program.
Methods: Naturalistic, observational, prospective cohort study. Outcome was measured by standardized assessment instruments. Stepwise, multivariate linear regression analysis was performed at discharge and the 6-month follow-up. Co-factors covered sociodemographics, comorbidities, social participation, affective health, and coping abilities.
Results: All regression models explained high proportions of the variance (53.3–72.1%). The corresponding baseline level was significantly associated to the change in every dependent variable at both follow-ups (explained variances: 11.4–22.8%). Pain relief significantly depended on improved function and vice-versa (5.9–14.8%) as well as on improved ability to decrease pain (9.6%). Functional improvement was significantly associated with decreased catastrophizing (19.4%) at discharge and decreased depression (20.5%) at the 6 month follow-up. Improvement in working capacity at the 6 month follow-up was significantly predicted by relieved pain (13.7%) and low catastrophizing (5.7%) at baseline.
Conclusion: Pain relief, improved physical function and working capacity were circularly dependent on each other. This is an empirical prove of the clinical experience and intuition. Coping, such as catastrophizing and ability to decrease pain, and depression act as important effect modifiers in this circle. These findings offer toe-holds for optimized therapy of chronic WAD.

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P 2

Articular hyper mobility in chronic lumbar pain: touching 10% of the patients

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Chronic lumbar pain is a relative frequent pain problem, with different etiologies: a great part is of no specific origin. Another part of the problem, is the presence of increased flexibility (named hypermobility), that may have a role in chronic pain patient.
The aim of this study is to analyze the prevalence of hypermobility in a low back pain patient group starting a multidisciplinary rehabilitation program, and the outcome results of a multidimensional treatment program
Method: We have studied the inclusion results of 550 of our patients that have accomplished a multi-disciplinary program and that have been followed over 24 months. The program contained physical training, occupational work hardening the hole in a cogntivo-comportemental approach.
We have analyzed the clinical signs for hypermobility in these patients according to the Beighton criteria, and also the evolution over 2 years comparing with the other low back pain patients.
Results: The prevalence of hypermobility(HMP) – according to the Beighton criteria – among our chronic lumbar pain population (CLP) was 9.8%, with a ratio of 3 men for 8 women. They have an increase in physical parameters similar as the global lumbar patients, but they started at a higher base level.
Conclusion: Hypermobility represents almost 10% of the patients in a rehabilitation program for chronic low back pain. They have physical base values that are quite better than the global population, but the clinical outcome doesn't really differ according work ability. But the rehabilitation program has to be adapted to their problems.

P 3

What is the best statistical test to calculate reproducibility in VFA reading in population-based cohort? A comparison between kappa of Cohen and Uniform Kappa

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Background: Gold standard to diagnose a Vertebral Fracture (VF) is X-ray. A new approach so called Vertebral Fracture Assessment (VFA) has been tested in clinical conditions. VFA seems to be adequate in term of reproducibility when compared with conventional X-rays in clinical situation. There is no evaluation of this method in screening population-based cohort. In all publications regarding reproducibility of VFA, the kappa test of Cohen is the most useful statistical test. Interpretation of kappa becomes precarious if class prevalence is extremely not uniform. This is the case in population-based cohort, where prevalence of the event is very low. To control it a new test of agreement has been recently proposed: the uniform kappa.
Objective: We aimed to calculate reproducibility in VFA reading in a screening population-based cohort by 2 different statistical tests: kappa of Cohen and uniform kappa
Method: We performed the reproducibility analysis on 360 OsteoLaus study patients randomly chosen. The OsteoLaus cohort concerns a sub population of women (50 to 80 yo) of the Lausanne cohort CoLaus. VFA were analyzed between T4 and L4. Two independent readers have read the 360 VFA to test inter-reading reproducibility. We calculated Kappas regarding the dichotomies criteria: readable vertebrae yes/no, vertebral fracture yes/no, ranking No readable/VFyes/VFno, for total VFA, dorsal spine and lumbar spine. We calculated Kappas for grade 0,1,2,3 and grouping grade (0 + 1, 2 + 3). We considered Landis and Koch values to interpret kappa of Cohen results (>0.81: excellent, 0.8–0.61: good, 0.6–0.21: moderate, 0.2–0: bad, <0: very bad). We estimated a good result of kappa uniform >0.75.
Results: 12% of vertebrae were not readable. Prevalence of VF varied from 3% to 4% (fracture/no fracture) for all vertebrae with 3 to 4% grade 1 VF, 0.6 to 1.3% grade 2 VF and 0.03% to 0.2% grade 3 VF. Inter-reader reproducibility by Kappa of Cohen was moderate to good (0.35 to 0.72) and good (0.74 to 0.98) by Uniform Kappa for all criteria.
Conclusions: VFA is well reproducible in clinical practice. In case of screening study, events are rare making the kappa of Cohen approach inappropriate in our opinion. We found that kappa of Cohen is considered as moderate. Uniform kappa is not influenced by the rate of events. We found that results of uniform kappa are high. In case of research/evaluation of general population, Uniform kappa seems more accurate for reproducibility than kappa of Cohen.

P 4

Giant cell tumour successfully treated by denosumab

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Background: Giant cell tumour (GCT) is a benign but locally aggressive primary osteolytic bone tumour, associated with skeletal morbidity and rare metastatic potential. Bone destruction by osteoclast-like giant cells is induced by an over-expression of RANK ligand (RANKL) by tumour cells. The efficacy of denosumab, a fully human monoclonal antibody against RANKL, has been described in GCT. We report two cases of patient with GCT in the distal radius, successfully treated by denosumab.
Cases: Case 1. A 28 years old carpenter male, good health, presented with a painful swollen left wrist. We observed swelling of the dorsal wrist, limitation of function, without neurovascular problem. X ray revealed an osteolytic lesion in the distal left radius. Biopsy confirmed the diagnosis of GCT, grade 3 according to the Enneking classification. Osteolytic progression was dramatically in 4 months time. Due to the proximity to the radio-carpal joint with advanced scalloping of subchondral and metaphyseal cortical bone, joint-salvage surgery was not possible. We initiated a treatment with denosumab (XGEVA), 120 mg/week for 1 month, followed by monthly injections. At 6 weeks, a significant decrease of pain and swelling was observed. A beginning recorticalization of eroded bone without progression of the size of the lesion was clearly noted on the X-Ray. No local or systemic side effects were observed. As a consequence, appropriate surgery is now possible. Case 2. A 25 years old man initially treated by surgery for a GCT of the right wrist presented signs and symptoms of local relapse 2 years after the initial management. A treatment with XGEVA was rapidly initiated (120 mg/week for 1 month). A spectacularly clinical improvement and radiological recorticalization were observed after 1 month of denosumab treatment. An appropriate surgery is under discussion.

Results: While surgery remains the treatment of choice for GCT, joint-salvage may not always be possible in cases with extensive epiphyseal involvement. The presence of osteoclast-like giant cells seems to make those lesions prone to the specific anti-RANKL treatment with denosumab, which is generally well tolerated. Denosumab appears to slow down tumour growth and promotes recorticalization of eroded bone. It might allow less aggressive and joint-salvage surgery in selected cases.

P 5

Changing The Awareness Of Low Vitamin D Status In A Rheumatologic Population: A Pre/Post-Study

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Background: Vitamin D reduces the risk of fall and fracture. Some experts recommend vitamin D level higher than 30 ng/ml (75 nmol/l) for high risk patients. We have shown that hypovitaminosis D was highly prevalent in our outpatient population (86% in 2009).
Objective: We then evaluated the evolution of vitamin D status in a similar population 2 years later (in 2011).
Method: One month-screenings were proposed in November 2009 and 2011 to all outpatients in our clinic. 25-OH vitamin D level was categorized as deficient (<10 µg/l), insufficient (10–30 µg/l) or normal (>30 µg/l). Patients who received any high dose of vitamin D3 6 months before each screening period were excluded. Patients not regularly seen at our outpatient clinic were also excluded.
Results: In 2011, 239 patients were included (230 in 2009) with a mean vitamin D level of 23.8 µg/l (4-53) (20.8 ng/ml in 2009, p = 0.0001). 4% had deficiency (8% in 2009), 68% insufficiency (79% in 2009), 28% normal results (13% in 2009). The same percentage of patients was on daily oral vitamin D in 2009 and 2011 (38%). Of these supplemented patients 51% had normal results in 2011 compared to 25% in 2009 (p <0.01). In the non vitamin D users 13% had normal results in 2011 compared to 6% in 2009 (p = 0.04). If we used the limit of 20 ng/ml rather than 30ng/ml as recommended by many experts, 52% patients had vitamin D levels >20 ng/ml in 2009 and 66% in 2011 (p = 0.001). During the two years of the study the number of 25-OH vitamin D dosages (4875 in 2009 and 6896 in 2011) and the prescription of high doses of vitamin D3 (116 in 2009 and 253 in 2011) increased in our hospital. In addition the number of publications and grand-round sessions about vitamin D had increased between 2009 and 2011.
Conclusions: Prevalence of hypovitaminosis D decreased in two years from 86% to 72%. These results were mainly due to the higher number of normal 25-OH vitamin D levels observed in patients taking oral daily vitamin D (increasing from 25% to 51%). These results seem related to: 1) better adherence to oral daily vitamin D in the supplemented patients; 2) better information of the physicians about hypovitaminosis D; 3) more frequent screening of vitamin D level and 4) higher prescription of high doses of vitamin D if needed.

P 6

Circulating polymorphonuclear granulocytes from rheumatoid arthritis patients demonstrate enhanced responsiveness and increased extrusion of NETs to stimulation with PMA and RA synovial fluid and serum.

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Introduction: Polymorphonuclear granulocytes (PMNs) are the most abundant immune cell population identified in the synovial fluid in the joints of patients with rheumatoid arthritis (RA), and seem to play a central role in the aberrant inflammatory response and destruction of the cartilage [1]. In response to certain stimuli, PMNs extrude their nuclear content in the form of nucleoprotein threads, known as extracellular traps (NETs), which possess various pro-inflammatory and immune-stimulatory characteristics [2].
Methods: PMNs from active RA patients and control subjects were exposed to PMA, a known chemical trigger of NET formation. Cl-amidine, a chemical PAD4 inhibitor, was applied for inhibition studies [3]. PMNs from healthy donors were incubated with serum and synovial fluid from RA patients. NET formation from RA and control neutrophils was assessed by combined immunostainings with anti-myeloperoxidase (MPO), anti-neutrophil elastase (NE), anti-PAD2 and -4, anti-cit-H3, anti-H1-core histones antibodies and DAPI as appropriate. Cell-free nucleosome levels were determined by ELISA, and protein location by Western blotting.
Results: Freshly isolated PMNs from RA patients showed an enhanced spontaneous NET release through the entire time course compared to the healthy controls. Intriguingly, the population of PMNs with delobulated/diffused nuclear phenotype was markedly higher in RA from the outset of measurement. RA PMNs exhibited even higher rates of NETosis and PAD4 nuclear translocation after chemical stimulation with PMA. The effect of PMA on NETosis was extensively inhibited by pre-treatment with Cl-amidine. Treatment of control neutrophils with either RA serum or synovial fluid also augmented the release of NETs compared to exposure to normal serum or synovial fluid from OA patients, respectively.
Conclusions: Basal PMN activation in RA is associated with enhanced spontaneous NET formation, and is further increased by PMA in a manner sensitive to inhibition of PAD4. It is also driven in vitro by serum and synovial fluid from RA patients. Further investigations are required in order to define the exact role of NET formation in the constant cross-talk between PMNs and adaptive immune responses in RA.

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P 7

Increased neutrophil granulocyte extracellular trap generation based on altered signalling provides a scaffold for auto-antigen induction in rheumatoid arthritis

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Introduction: Rheumatoid arthritis (RA) is an inflammatory, erosive disorder of the joints often characterised by anti-citrullinated peptide antibodies (ACPAs) in the serum [1]. While ACPAs have been associated with increased inflammation, joint destruction and reduced response to therapy, the mechanisms leading to the citrullination of arginine residues by peptidyl arginine deiminase (PAD) 2 and 4 have remained unclear. PAD4 in polymorphonuclear granulocytes (PMNs), the predominant leukoctyes in RA synovial fluid, is critical for neutrophil extracellular trap (NET) formation [2, 3]. In this study, we investigated the signaling pathway leading to histone modification and NET extrusion in RA neutrophils.
Methods: PMNs were isolated from RA patients with active disease and healthy controls. Reactive oxygen species (ROS) production was evaluated by FACS utilizing a DCFH-DA assay. Spontaneous NET formation from RA and control neutrophils was assessed through time course experiments and by scanning electron and fluoresence microscopy. Combined immunostainings with anti-myeloperoxidase (MPO), anti-neutrophil elastase (NE), anti-PAD2, anti-PAD4, anti-citH3, anti-H1-core histones antibodies and DAPI were applied for in depth cellular analysis. Protein and RNA quantities and subcellular locations were determined by Western and Northern blotting, respectively.
Results: PMNs from RA cases showed increased spontaneous NET formation *in vitro*, which was associated with elevated ROS production, enhanced NE and MPO message and protein expression, and nuclear translocation of PAD4. Nuclear morphology indicated a significantly higher activation state of RA PMNs. PAD4 was detected together with PAD2 along with citrullinated histone (citH3) and DNA on extruded NETs. NET-associated MPO activity was markedly elevated in RA cases versus controls.
Conclusions: Signaling elements associated with the initiation and extrusion of NETs are significantly altered towards NET formation, which is vastly increased compared to healthy controls. The extracellular presence of PAD2 and PAD4 on extruded NETs represents a potential mechanism for aberrant citrullination of relevant proteins and peptides. Hence, these findings provide an explanation for *in vivo* autoantigen citrullination as a basis for ACPA induction, and implicate PMNs as key upstream players in the pathogenesis of RA.

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P 8

A 18-year-old woman with polyarthritis, anterior uveitis and coronary vasculitis: a case of Kawasaki disease of the adult

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Background: Kawasaki disease (KD) is a multisystemic vasculitis accompanied by skin, ear-nose and throat, ocular, lymph nodes and joint manifestations. The highest incidence of this disease is found in the asian paediatric population. KD is 20-times less frequent in the pediatric caucasian population. 91 cases have been reported in the literature since 1979 in adults and therefore KD is a rarity in this category of patients.
Objective: To report the case of a 18-year-old woman with KD of adult onset.
Case report: A 18-year-old woman presented to the emergency room with odynodysphagia and fever. She had been treated as an out-patient with amoxicilline/clavulanate per os for sore throat. One week later, she returned to the emergency room with multiple joint and cervical pain, interscapular pain and jaw claudication. Clinically, a polyarthritis, a discrete maculo-papulous rash of the lower limbs, injected conjunctivae, cervical adenopathy and a diastolic murmur were observed. Blood pressure was normal in both arms. The most important laboratory values are: ESR >110 mm/h, CRP 180 mg/l, haemoglobin 90 g/l with normal MCV and MCH, leucocytes 23 G/l and thrombocytes 620 G/l. CK, troponin and BNP were normal. Leucocytes were present in urine. Immunological investigations were non contributive. Serological and exhaustive microbiological examinations were negative. Ophthalmological examen revealed bilateral anterior uveitis. Ultrasound examination of the extra-thoracic arteries was normal and the US examination of the heart showed a discrete pericardial effusion. The ECG was normal. An angio-CT examination of thoracic and abdominal arteries showed isolated proximal aneurysms of all the 3 main coronary arteries. A diagnosis of KD was made and she responded rapidly to treatment with intravenous immunoglobulin and steroids. Weeks later she developed palmar desquamation.
Conclusion: KD – even if it is a rare disease in the adults – has to be considered in the differential diagnosis of diseases with multisystemic inflammatory manifestations including a specific coronary vessels disease with aneurysms.

P 9

Structural differences between anti-TNF agents are associated with dissimilar rates of secondary loss of effectiveness

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Introduction: Differences in drug survival between anti-TNF agents (aTNF) have been attributed to variations in molecular structure leading to increased immunogenicity, in particular between chimeric and fully human monoclonal antibodies (MABs) and between MABs and soluble receptor antagonists (CEPTs). Synthetic DMARDs, such as methotrexate, have shown to delay the development of anti-drug antibodies and increase aTNF retention. Faced with secondary loss of effectiveness, clinicians may increase drug dosage, initiate new co-therapies (glucocorticoids, other DMARDs) or discontinue aTNF. The aim of this study was to investigate the time until aTNF drug adjustments attributable to secondary loss of effectiveness.
Methods: All pts who have received a first dose aTNF were retrieved from the SCQM cohort. The primary end point was drug adjustments attributable to aTNF secondary loss of effectiveness, which was operationally defined as a composite of (1.) aTNF discontinuation due to ineffectiveness occurring after, (2.) aTNF dose increase (in frequency or in total dose) or (3.) a major increase in co-therapy (initiation of – or doubling in the dose of – DMARD cotherapy or oral glucocorticoids) occurring after 6 months of aTNF therapy. The primary exposure of interest was the type of aTNF agent, specifically MAB aTNFs (Infliximab, Adalimumab, Golimumab) versus CEPTs (Etanercept). We performed a 'time-to-event analysis' using a Cox proportional hazards model, adjusting for potential confounders.
Results: We identified 4796 treatment courses of aTNF therapy (3116 with MABs and 1680 with CEPTs), 1626 drug adjustments attributable to aTNF secondary loss of effectiveness (819 increases in co-therapy, 579 aTNF discontinuations, 180 aTNF dose increase) contributing a total of 7185 patient-years of aTNF use. No major differences existed in baseline characteristics, except for more pts on aTNF monotherapy in the CEPT group (28% vs 18%, p <0.01) and more pts on MTX in the MAB group (64% vs 54%, p <0.01).
The overall incidence of drug adjustments attributable to aTNF secondary loss of effectiveness was higher in the MAB group (adjusted Hazard Ratio (HR) for MABs: 1.21 [95% CI: 1.09–1.34]) than in the CEPT group. The median crude drug survival was 30 months (IQR: 14–70) for MABs and 36 months (IQR: 15–88) on CEPTs.
Conclusion: Drug adjustments attributable to secondary loss of effectiveness occur significantly more frequently with MAB than with CEPT aTNF agents.

P 10

Comparison of causes of drug discontinuation between anti-TNF agents and 'non-anti-TNF biologic agents' in anti-TNF inadequate responder RA patients

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Introduction: After failure of a anti-TNF agent (aTNF), clinicians may choose to prescribe an alternative aTNF or switch to a 'non-aTNF biologic antirheumatic agent' (non-aTNF-BIO; Abatacept (ABA), Rituximab (RTX), Tocilizumab (TCZ)). It has been previously shown that non-aTNF-BIO have a better overall drug retention compared to alternative aTNF, but no direct comparison of their respective effectiveness and safety has been made.
The aim of this study was to compare drug retention rates of non-aTNF-BIO with alternative aTNF, as groups, prescribed in second or third intention and to compare specifically drug discontinuation due to ineffectiveness or adverse events (AEs); and to analyze these outcomes for individual biologic agents.
Methods: This cohort study (SCQM-RA) analyzed all patients treated with an alternative biological, after a first inadequate response to an anti-TNF agent (ineffectiveness in 50%, AE in 33%). The primary end points are discontinuation rates (i) for ineffectiveness and (ii) for intolerance (AEs leading to treatment discontinuation). Time to discontinuation was defined as the time between drug initiation and last administration plus one dispensation interval. Because RTX may be administered 'on demand' with flexible intervals, we defined RTX discontinuation as a major alteration of the antirheumatic regimen after RTX initiation or time of last infusion plus six months, whatever happened 1st. Drug discontinuation was analyzed using a Cox proportional hazards model, adjusting for potential confounders.
Results: We identified 2391 biologic treatment courses in aTNF inadequate responders (*1,199* with an alternative aTNF and *1,192* with a biologic agent of a different mode of action) and 1203 treatment discontinuations. A second biological was administrated 1507 times, a third – 587, a fourth or fifth – 297 times, contributing a total of 3554 patient-years on biological agents. No major differences existed in baseline characteristics, except for a larger number of previous biologic failures (median of 2 versus 1, p <0.001) and slightly older ages, longer disease durations in the non-aTNF-BIO group.
The overall drug discontinuation was higher in the aTNF group than in the non-aTNF-BIO group. The median crude drug survival was 9.0 months (IQR: 7.4–11.9) for alternative anti-TNFs and 18.0 (IQR: 13.9–22.7) months for non-aTNF-BIOs (adjusted Hazard Ratio (HR) for aTNF: 1.96 [95% CI: 1.71–2.26]). Drug discontinuation for ineffectiveness (N = 710, HR for aTNF: 1.74 [95% CI: 1.46 – 2.08]) and for AEs (N = 279, HR for aTNF: 2.09 [95% CI: 1.58–2.77]) were higher with alternative aTNF than with non-aTNF-BIOs, while no significant differences were found for other reasons of discontinuation (remission, pregnancy…). While a trend to lower drug discontinuation was observed with all agents within the non-aTNF-BIO group, the effect was significantly stronger with RTX (HR for ineffectiveness: 0.44 [99% CI: 0.33–0.60); HR for AEs: 0.34 [99% CI: 0.20–0.57]), which may be partially explained by a completely different approach of administration.
Conclusion: In patients having experienced an inadequate response to a previous anti-TNF agent, biologic agents with a different mode of action appear to have significantly lower drug discontinuation rates than alternative anti-TNF agents, for both ineffectiveness and for AEs.

The numbers refer to the pages of this supplement.