because we have also demonstrated that the overexpression of HAS2 (HAS2-OE) exerted the same chondroprotective effects on human and bovine chondrocytes. Others [2] have reported that HAS2-OE in tumor cells generates a flux in intracellular UDP-sugar pools that resulted in changes in cell metabolism; switching from a dependence on glycolysis to aerobic respiration. HAS2-OE and 4-MU likely also cause dramatic fluxes in intracellular UDP-GlcUA pools. From these results, we hypothesized that the effect of HAS2-OE and 4-MU relate to changing metabolism and the possibility of inhibition of glycolysis induce chondroprotective effect. To determine that, we used the glycolysis inhibitor, 2-Deoxyglucose (2DG) as an alternative agent to change metabolism in chondrocytes.

Objectives: The objective of this study was to investigate the mechanism of chondroprotective effects of 2DG

Methods: Bovine and human chondrocyte were stimulated with IL-1 β (2ng/ml) in the presence or absence of 4MU (1.0mM), 2DG (0.2-20mM). Bovine chondrocytes were tested using Seahorse Flux Analyzer (Agilent Tech) to determine rate changes in medium accumulation of +H protons (indicative of lactic acid accumulation: ECAR) and for O₂ consumption (indicative of mitochondrial respiration: OCR). Accumulation of MMP13 and phosphor AMPK (pAMPK) protein was quantified with Western blotting. Human and Bovine cartilage explants were cultured with L-1 β in the presence or absence of 2DG (20mM) and d 5-Aminimidazole-4-carboxamide 1- β -D-ribofuranoside (AICAR) to pharmacologically induce AMPK for 7 days and stained with Safranin O.

Results: Reduced mitochondrial potential and enhanced dependence on glycolysis was observed in IL-1 β stimulated chondrocytes. Co-treatment with 4-MU and 2DG returned the cell metabolism to levels at or below baseline (Fig 1A, B). The Seahorse ATP Rate Assay means the contributions of glycolysis and mitochondrial respiration to chondrocyte ATP production (Fig 1C). In control chondrocytes, the use of glycolysis contributes to the majority of ATP produced (grey bars) approximately 1/5th from the TCA cycle (red bars). IL-1 β -activated chondrocytes display increase in glycolysis and decrease in mitochondrial contributions. These changes are reversed by co-treatment with 4MU and 2DG. As shown in Figs 2A, 2DG reversed the IL1 β -induced increases accumulation of MMP13 protein in human OA chondrocytes by Western blotting analysis. Although IL-1 β lost safranin O staining in human and bovine samples, co-incubation with 2DG blocked in the loss of proteoglycan (Fig 2B). pAMPK is associate with energy homeostasis in chondrocytes. IL-1 β treatment decreased accumulation of phosphor AMPK. Co-treatment with 4-MU and 2DG resulted in a rescue of the pAMPK status (Figure 3A). Co treatment with AICAR, which is inducer of AMPK, also blocked in the loss of proteoglycan (Fig 3B).

FIGURE 1 Bovine chondrocytes were incubated 24h $\pm$ IL1 β (2 ng/ml) and without or with 4MU (1.0mM) or 2DG (2.0 mM). **Panel A** depicts a representative Mito Stress Test wherein bars represent basal and maximal mitochondrial respiration as a corrected OCR value. **Panel B** show summaries of ECAR data representative of changes in basal glycolysis rates as labeled. **Panel C** show a representative ATP rate assay wherein the contribution of glycolysis (grey bars) and mitochondrial respiration (red bars) to ATP production. (**: p<0.01 ***: p<0.001)

FIGURE 2 Effect of 2DG on chondrocytes activated with IL- β . **Panel A** represent the experiment with human OA chondrocytes treated $\pm$ 2 ng/ml IL1 β in the absence or presence of 0.2, 2.0 or 20 mM 2DG for 24h. **Panel B** depict representative examples of bovine and human OA cartilage explants stained by Safranin O.

FIGURE 3 The effect of 4MU and 2DG on p-AMPK changes in IL1 β activated chondrocytes.

Panel A: Bovine chondrocytes were treated for 24 h without (Ctr) or with IL1 β (2 ng/ml) and $\pm$ 2DG (2.0 mM), $\pm$ 4MU (0.5 mM).

Panel B depict representative examples of bovine cartilage explants stained by Safranin O treatment with AICAR or not.

Conclusion: 4-MU and 2DG have chondroprotective effect by changing metabolism and upregulate AMPK. We propose that 4MU and 2DG become useful when these endogenous responses are not enough to rescue cells from a pro-catabolic phenotype.

References:

[1] J. Biol. Chem. 291:12087, 2016; [2] J. Biol. Chem. 291:24105, 2016

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Biological DMARDs in RA II

OP0208 PATIENTS REPORT FATIGUE AS AN ADVERSE DRUG REACTION OF BIOLOGICS

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Background: Chronic fatigue is a well-known symptom in patients with rheumatic diseases and other immune-mediated inflammatory diseases (IMIDs). Therefore, fatigue as an adverse drug reaction (ADR) to biologics may remain unrecognised or may erroneously be attributed to the disease.

Objectives: To assess patient-reported fatigue attributed to biologics for IMIDs and investigate predisposing factors of patient-reported fatigue.

Methods: The Dutch Biologic Monitor is a multicenter patient-reported ADR monitoring system that surveys patients using a biologic for an IMID. Patients completed web-based questionnaires regarding ADRs attributed to biologics and the course and experienced burden (5 point Likert scale) of these ADRs. All patient-reported ADRs with MedDRA Preferred Term 'fatigue' were defined as biologic-associated fatigue (BA-fatigue). Basic demographics and treatment characteristics were compared between patients reporting BA-fatigue and patients not reporting BA-fatigue (reported other ADRs or no ADRs).

Results: Out of 1369 participating IMID patients, 696 patients reported 1844 unique ADRs. BA-fatigue was reported by 100 patients and 48 patients described a consistent pattern of recurring fatigue after each administration. Most of these patients (88%) described recovery from BA-fatigue within one week after biologic administration and 73 patients reported health care

professional (HCP) contact following BA-fatigue, with dose adjustment in 8 and discontinuation in 5 patients. Basic demographics and characteristics that differ significantly between patients reporting BA-fatigue and patients not reporting BA-fatigue are summarized in table 1. No significant difference was found for other biologics, IMiDs, combination therapy and comorbidities. BA-fatigue was reported by 27% of rituximab users (n=33), 27% of vedolizumab users (n=26), 16% of tocilizumab users (n=50), 14% of infliximab users (n=159) and 3% of etanercept users (n=418). Although 29 patients in the BA-fatigue population had RA and 29 patients had Crohn's disease (CD), 571 patients in our overall study population had RA and 194 patients had CD, suggesting BA-fatigue was reported by CD patients more often. The mean burden of BA-fatigue was higher than the mean burden of other ADRs ($p < 0.001$).

Table 1. Characteristics of patients with BA-fatigue compared to patients with other ADRs and without ADRs

	n	Patients with BA-fatigue n (%)	Patients with other ADRs n (%)	Patients without ADRs n (%)
		100 (100%)	596 (100%)	673 (100%)
Basic demographics				
Age (years) (mean $\pm$ SD)		50.0 $\pm$ 14.6	53.4 $\pm$ 13.6 *	55.7 $\pm$ 14.2 ***
Gender (Female)		59 (59%)	398 (67%) ^{ns}	342 (51%) ^{ns}
Smoking n (%)		25 (25%)	97 (16%) *	100 (15%) *
BMI (kg/m ²) (mean $\pm$ SD)		25.7 $\pm$ 4.4	25.9 $\pm$ 4.7 ^{ns}	26.6 $\pm$ 5.5 ^{ns}
Biologic				
Infliximab		22 (22%)	53 (9%) ***	84 (12%) *
Etanercept		13 (13%)	177 (30%) ***	228 (34%) ***
Rituximab		9 (9%)	18 (3%) **	6 (1%) ***
Tocilizumab		8 (8%)	29 (5%) ^{ns}	13 (2%) **
Vedolizumab		7 (7%)	12 (2%) *	7 (1%) ***
IMiD				
Rheumatoid arthritis		29 (29%)	270 (45%) **	272 (40%) *
Crohn's disease		29 (29%)	77 (13%) ***	88 (13%) ***
Other indication		16 (16%)	53 (9%) *	39 (6%) ***
Combination therapy				
Methotrexate		23 (23%)	167 (28%) ^{ns}	227 (34%) *
Comorbidity				
Psychiatric disorder		11 (11%)	49 (8%) ^{ns}	31 (5%) *
Other comorbidity		30 (30%)	124 (21%) *	102 (15%) ***
Mean burden of ADR $\pm$ SD		2.9 $\pm$ 0.9	2.4 $\pm$ 1.1 ***	

Mann Whitney U, independent t-test and Fisher's exact as appropriate

ns: not significant * $p \leq 0.05$ ** $p \leq 0.01$ *** $p \leq 0.001$

Conclusion: HCPs should be aware that fatigue may be associated with biologic therapy and has a significant burden on patients. Evaluating the course of the symptoms might be helpful in recognizing BA-fatigue.

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OP0209

INTERVAL PROLONGATION IN ETANERCEPT-TREATED PATIENTS WITH RHEUMATOID ARTHRITIS, ANKYLOSING SPONDYLITIS OR PSORIATIC ARTHRITIS: AN OPEN-LABEL, RANDOMISED CONTROLLED TRIAL

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Background: The majority of patients with a rheumatic disease treated with etanercept may be overexposed. Data regarding etanercept tapering is scarce, particularly in psoriatic arthritis (PsA) and ankylosing spondylitis (AS). Dose reductions can potentially reduce blood drug levels too much, resulting in loss of effect.

Objectives: We compared extending the dose interval to continuation of the standard dose and studied the success rate of etanercept discontinuation. Etanercept concentrations were measured throughout the study.

Methods: 160 consecutive patients with rheumatoid arthritis (RA), PsA or AS with sustained minimal disease activity (MDA) were enrolled in this 18-month, open-label, randomised controlled trial. The intervention group doubled the dosing-interval at baseline and discontinued etanercept 6 months later. The control group continued the standard dose up to 6 months, after which the dosing-interval was doubled. Primary outcome was the proportion of patients maintaining MDA after 6 months follow-up.

Results: At 6 months, MDA status was maintained in 47 (63%) patients in the intervention group and 56 (74%) in the control group ($p=0.15$), with comparable results in all rheumatic diseases. Median etanercept concentrations decreased from 1.50 $\mu\text{g/mL}$ (25-75th percentile 1.06-2.65) to 0.46 $\mu\text{g/mL}$ (0.28-0.92) after 6 months of interval prolongation (figure 1). In total, 40% discontinued etanercept successfully with maintained MDA for at least 6 months.

Figure 1. Median (with Q1 to Q3 boxplots) etanercept concentrations (per protocol) during the first 6 months of follow-up in the intervention group (prolongation; gray boxplots) and the control group (continuation; white boxplots), separated by disease (RA, PsA, AS). Bars represent 10-90 percentile and outliers are shown separately (dots).

Conclusion: As observed in RA, etanercept tapering can be safely attempted in PsA and AS patients in sustained MDA. A substantial proportion of patients could stop etanercept for at least 6 months. In many patients low drug concentrations proved sufficient to control disease activity. However, the risk of minor and major flares is substantial, even in patients continuing standard dosing.

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