determine their functional interplays. Protein-protein interaction assays were performed to detect the interactions of ADAMTS-12 with CTGF

Results: ADAMTS-12^{-/-} mice are more susceptible to collagen-induced arthritis. Accelerated disease onset, significant increase in the arthritis score and arthritis incidence, were observed in ADAMTS-12^{-/-} mice (figure 1a). Histological analysis of whole ankle joints demonstrated a significant increase in synovitis, destruction of bone and cartilage loss in ADAMTS-12^{-/-} mice. ELISA results indicated that ADAMTS-12^{-/-} CIA mice exhibited enhanced release of pro-inflammatory and reduced secretion of anti-inflammatory cytokine. Collectively, these data demonstrate that ADAMTS-12^{-/-} renders mice highly susceptible to CIA.

ADAMTS-12 interacts with and cleaves CTGF, and ADAMTS-12-mediated signalling depends on CTGF during inflammation. It is known that CTGF plays a pro-inflammatory role in the pathogenesis of inflammatory arthritis. We co-transfected CTGF and ADAMTS-12 into 293 T cells and found ADAMTS-12 bound to (figure 1b) and digested CTGF (figure 1c). *In vivo* studies also demonstrated that CTGF was accumulated in the synovium of ADAMTS-12^{-/-} CIA mice. To further determine whether CTGF is a critical regulator of ADAMTS-12 mediated signalling, we generated CTGF deficient Raw264.7. Overexpression of ADAMTS-12 and CTGF deficiency could decrease the activation of inflammatory signalling markers such as NFκB, p38 and JNK in response to IL-1β at a comparable level. More importantly, overexpression of ADAMTS-12 in CTGF deficient Raw264.7 failed to further inhibit the activation of these signal molecules as compared to CTGF deficient Raw264.7 (figure 1f). Taken together, these results suggest that CTGF is a critical regulator of ADAMTS-12 mediated signalling during inflammation.

Blocking CTGF attenuates inflammatory arthritis in ADAMTS12-deficient CIA mice model. To determine whether the accelerated inflammation in ADAMTS-12^{-/-} mice resulted from the accumulated CTGF, we administered CTGF antibody to ADAMTS-12^{-/-} CIA model after disease onset. The arthritis score in ADAMTS-12 deficient mice was significantly reduced in presence of CTGF antibody (figure 1d). Moreover, histological analysis indicated CTGF abrogated further tissue destruction and inflammation (figure 1e).

Abstract OP0224 – Figure 1 ADAMTS-12 protects against inflammatory arthritis through interacting with CTGF. (a) Clinical arthritis scores in WT and KO CIA mice. (b) Co-IP assays detect the associations of ADAMTS-12 with CTGF. (c) Western blotting of CTGF cleavage by ADAMTS-12. (d) Clinical arthritis scores in WT, control IgG-treated KO and CTGF antibody-treated KO mice with CIA. (e) Safranin O staining. (f) WT or CTGF-deficient (CTGF-def) Raw264.7 were transfected with pcDNA-ADAMTS 12 for 48hrs, then cells were treated with or without IL-1β for indicated time. Cell lysate were separated in SDS-page and probed with indicated antibodies.

Conclusions: ADAMTS-12-mediated regulation of inflammatory arthritis is probably through, at least in part, its interplay with CTGF and blockage of CTGF has been shown to be effective in treating inflammatory arthritis.

Disclosure of Interest: None declared

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OP0225 S100A9 MEDIATES ACUTE NOCICEPTIVE PAIN IN EXPERIMENTAL SYNOVITIS

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Background: Synovitis-associated pain is an important aspect of arthritis pathology. Several inflammatory mediators released by the synovium have been implicated in the regulation of pain, including S100A8 and S100A9. These mediators may regulate pain either via direct stimulation of TLR4 on the nerve endings in the synovium or via stimulation at the site of the dorsal root ganglia (DRG), thereby enabling an increased phagocyte infiltration that may cause sensitisation.

Objectives: To elucidate the role of S100A9 in the pain response after induction of an acute synovitis using streptococcal cell walls (SCW) as a trigger, by comparing S100a9^{-/-} mice and their wild type controls.

Methods: Acute synovitis was induced by a single intraarticular injection of SCW in the knee joint of C57Bl/6 (WT) mice and S100a9^{-/-} mice (also functional knock-outs for S100A8). Control mice received a saline injection. Serum S100A8/A9 levels were investigated by ELISA. Joint swelling and cell influx was assessed by ^{99m}Tc accumulation and histology. Pain response were investigated using an Incapacitance Tester (weight bearing), Catwalk (gait analysis) and von Frey's filaments (mechanical allodynia). Gene expression of inflammatory mediators and neuron activation markers in DRG were determined by q-PCR. Monocyte influx and protein expression was monitored by immunohistochemistry (IHC).

Results: A single intraarticular injection of SCW resulted in acute synovitis, accompanied by a strongly increased synovial expression of S100A8 and S100A9 and increased serum S100A8/A9 levels at day 1, which returned to basal levels at day 7. However, joint swelling and cell influx were similar in WT and S100a9^{-/-} mice at day 1, excluding a role for S100A8/9 on pain perception via increased synovitis. WT mice showed a marked and significant decrease in the percentage of weight bearing on the SCW injected hind paw (28%) compared to saline injection (47%, p<0.001) at day 1, whereas S100a9^{-/-} mice did not. In addition, the stand-phase of the unaffected paws was significantly increased in WT mice 1 day after injection, while in S100a9^{-/-} mice these parameters were not altered. Both mouse strains showed a similar reduction of paw withdrawal threshold, excluding a role for S100A8/9 in allodynia. Analysis of DRG showed no increased phagocyte infiltration after SCW injection and no change in gene expression of the chemokines MCP-1 and KC (for monocytes and neutrophils respectively), and pro-inflammatory cytokines IL-1β and TNF was measured. In addition, F4/80 staining was comparable between WT and S100a9^{-/-} mice. However, expression of the neuron activation markers NAV1.7, ATF3 and GAP43 was significantly increased at 1 day after SCW injection in WT mice as compared to saline injected mice (p=0.022, 0.004 and 0.030 respectively) while no regulation of these factors was found in S100a9^{-/-} mice, which is in line with the reduced pain response observed earlier in S100a9^{-/-} mice. The difference in NAV1.7 expression in the DRG was further confirmed at protein level with IHC.

Conclusions: These findings show that S100A9 is an important mediator of inflammatory nociceptive pain response in the knee, rather than being involved in peripheral sensitisation. During the acute phase of inflammation S100A8/A9 is likely regulated via direct activation of TLR4 on nerve endings in the synovium and not via monocyte infiltration in the DRG.

Disclosure of Interest: None declared

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Biologics in RA. More, more and more about safety.

OP0226 RISK OF HOSPITALISED INFECTION AND INITIATION OF ABATACEPT VERSUS TNF INHIBITORS AMONG PATIENTS WITH RHEUMATOID ARTHRITIS: A PROPENSITY SCORE-MATCHED COHORT STUDY

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Background: Rheumatoid arthritis (RA) patients receiving biologic therapy are at an increased risk of infection. TNF inhibitors (TNFi) and abatacept are used similarly in RA as the first line biologic. Few studies conducted a head-to-head

Abstract OP0226 – Table 1. Risk of hospitalised infection in Abatacept versus TNFi initiators: PS-matched analysis

		Event	Abatacept (n=11,248)			Event	TNF inhibitors (n=11,248)		
			Person-years	IR	HR (95% CI)		Person-years	IR	HR (95% CI)
Primary outcome	Hospitalised infection	1024	25 591	40.01	0.97 (0.89–1.06)	1031	25 021	41.21	1.0
Secondary outcomes	Bacterial infection	635	26 475	23.99	1.04 (0.93–1.16)	598	25 891	23.10	1.0
	Herpes zoster	402	26 686	15.06	1.01 (0.88–1.16)	391	26 177	14.94	1.0
	Bone/joint infection	53	27 390	1.93	1.33 (0.88–2.01)	39	26 862	1.45	1.0
	Cardiac infection	0	27 511	0	-	3	26 925	0.11	1.0
	Gastrointestinal infection	158	27 208	5.81	1.21 (0.96–1.52)	128	26 705	4.79	1.0
	Genitourinary infection	130	27 279	4.77	1.20 (0.93–1.55)	106	26 725	3.97	1.0
	Respiratory infection	351	26 777	13.11	0.91 (0.79–1.05)	378	26 163	14.45	1.0
	Skin/soft tissue infection	178	27 168	6.55	0.92 (0.75–1.13)	189	26 546	7.12	1.0
	Neurologic infection	2	27 504	0.07	0.20 (0.04–0.90)	10	26 911	0.37	1.0

comparison of infection risk specific to different types of biologics used in a real-world setting.

Objectives: To evaluate the risk of hospitalised infection among RA patients who initiate abatacept versus TNFi.

Methods: We identified RA patients aged ≥ 18 years with ≥ 2 RA diagnoses separated by 7–365 days using insurance claims data from Truven MarketScan database (2005–2015). New users of abatacept or TNFi (adalimumab, etanercept, certolizumab, golimumab, and infliximab) were included. To balance RA duration or severity between the groups, we excluded patients who previously used rituximab, tocilizumab or tofacitinib. We also excluded patients with malignancy, dialysis, HIV/AIDS, or organ transplantation. The primary outcome was a composite endpoint of hospitalised infection including bacterial, viral or opportunistic infection. Secondary outcomes were bacterial infection, herpes zoster, and infections affecting different organ systems. To control for over 50 baseline confounders, we performed 1:1 propensity score (PS) matching. We estimated incidence rate (IR) and hazard ratio (HR) with 95% confidence interval (CI) of risk of hospitalised infection.

Results: We included 11,248 PS-matched pairs of abatacept and TNFi initiators with median age of 56 years. 83% were female. In the 1 year baseline period, 68% had any use of oral steroids and 55% used methotrexate. 18% had diabetes and 3% had hospitalised infection. Over the mean 2.3 year of followup, 1024 abatacept and 1,031 TNFi initiators were hospitalised for infection (table 1). The risk of any hospitalised infection was similar (HR 0.97, 95% CI: 0.89 to 1.06) between the two groups with the IR per 1000 person-years of 40.01 in abatacept and 41.21 in TNFi initiators. We found consistent results in the analyses of secondary outcomes. IR=events per 1000 person-years

Conclusions: In this large cohort of RA patients who used abatacept or TNFi as a first or second-line biologic agent, we found no difference in the risk of hospitalised infection between the two groups.

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OP0227 TIMING OF ABATACEPT BEFORE ELECTIVE ARTHROPLASTY AND POST-OPERATIVE OUTCOMES

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Background: Guidelines recommend holding biologic DMARDs before major surgery, but few studies have examined perioperative timing of individual biologic therapies.¹

Objectives: We aimed to determine whether holding abatacept infusions before elective hip or knee arthroplasty is associated with lower risk of adverse post-operative outcomes.

Methods: This retrospective cohort study using U.S. Medicare claims data from 2006–September 2015 evaluated adults with ≥ 2 ICD9 codes for RA who received abatacept by infusion within 6 months of inpatient primary or revision total hip or knee arthroplasty. Infusions were selected as these procedures can be precisely dated in claims data. Patients with hip fracture, malignancy, pre-existing infection, non-elective procedures, or surgery after hospital day 3 were excluded. Logistic and Cox regression were used to assess associations between abatacept stop timing (time between most recent infusion and surgery in 4 week intervals based on dosing interval) and adverse outcomes: 1) hospitalised infection within 30 days (from discharge diagnoses, PPV >80%), 2) rate of prosthetic joint infection (PJI, ICD9 996.66) within 1 year, and 3) 30 day readmission (among patients with discharge to home, rehabilitation facility, or skilled nursing facility). Propensity scores based on the probability of being in each abatacept stop timing group were used to balance confounders across exposure groups using inverse probability weighting. Risk of hospitalised infection associated with methotrexate or with average glucocorticoid dose in the 3 months prior to surgery was assessed in abatacept treated patients using a reduced multivariable logistic regression model.

Results: Among 1537 surgeries in 1410 patients, there were 158 (10.3%) hospitalised infections within 30 days (most commonly urinary, skin/soft tissue, and pneumonia), 34 (2.6/100 person-years) PJI within 1 year, and 108/1448 (7.5%) 30 day readmissions. There were no significant differences in the rates of hospitalised infection, prosthetic joint infection, or 30 day readmission in patients who received abatacept within 4 weeks of surgery vs patients with longer stop timing (table 1). Among abatacept treated patients, glucocorticoid use (vs. none) was associated with a dose-dependent increase in the risk of hospitalised infection: ≤ 5 mg [aOR 1.32 (0.88–1.98)], 5–10 mg [aOR 2.40 (1.54–3.73)], >10 mg [aOR 1.73 (0.74–4.06)]. Concomitant use of methotrexate was not associated with hospitalised infection risk [aOR 0.97 (0.68–1.38)] (table 2).

Abstract OP0227 – Table 1 Association between abatacept stop timing and post-operative outcomes, from logistic and Cox regression with inverse probability weighting

Abatacept Stop Timing	30-day hospitalized infection		Prosthetic joint infection within 1 year		30-day readmission*	
	N (%)	aOR (95% CI)	N (inc/100py)	aHR (95% CI)	N (%)	aOR (95% CI)
< 4 weeks (n = 594)	61 (10.3)	Reference	11 (2.4)	Reference	44/572 (7.7)	Reference
4-8 weeks (n = 670)	60 (9.0)	0.98 (0.66-1.45)	15 (3.1)	1.22 (0.55-2.73)	45/627 (7.2)	0.97 (0.62-1.53)
≥ 8 weeks (n = 273)	37 (13.6)	1.11 (0.69-1.79)	6 (3.0)	0.71 (0.25-2.03)	19/249 (7.6)	0.94 (0.51-1.73)

*Readmissions assessed among patients with discharge to home, rehabilitation facility, or skilled nursing facility. Adjusted odds ratios (aOR) and hazard ratios (aHR) from logistic and Cox regression with inverse probability treatment weights. Inc/100py = incidence per 100 person years.