SAT0246

TARGETING JAK/STAT PATHWAY IN TAKAYASU'S ARTERITIS

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Background: Takayasu's arteritis (TAK) is a large vessel vasculitis (LVV) in which the aorta and its main branches are greatly inflamed, leading to wall thickening, fibrosis, stenosis and to artery occlusion(1). The disease is more common in women mostly between 20 and 30 years old. TAK has a high morbidity rate: 50% of patients will relapse within 10 years after diagnosis(2, 3). This inflammation is essentially mediated by infiltration with macrophages and pro-inflammatory Th1/Th17 effector subsets(4–8). But the mechanisms behind these phenomena are essentially unknown. TAK is mainly treated with non-specific steroids(1) which are associated with potential side effects when used for a long-time course.

Objectives: Our work aims to explore the involvement of JAK/STAT signaling pathway and its downstream biological cascades in pro-inflammatory T cells differentiation and disease activity of TAK. Plus, our work allows to consider targeting the JAK/STAT pathway in TAK using JAK inhibitors (JAKinibs).

Methods: We analyzed transcriptome of FACS-sorted CD4+ and CD8+ T cells from healthy donors (HD) and TAK, using differential gene, pathway and network analysis. Then, we assessed in vitro and in vivo effects of JAKinibs in TAK by flow cytometry (FC).

Results: Transcriptome analysis showed hundreds of significantly dysregulated genes/pathways for CD4+ and CD8+ samples between HD and TAK. Among these, we noticed in TAK a great enrichment for pathways linked to type I and II interferons (IFN), JAK/STAT and cytokines/chemokines-related signaling. We confirmed by RT-qPCR the upregulation of a type I IFN-specific gene signature in TAK T cells as compared to HD. Using genes coming from the previous pathways, we constructed networks connecting them according to their respective protein interactions. This representation showed for both CD4+ and CD8+ T cells that JAK and STAT genes were densely connected, thus representing core genes/proteins in the TAK physiopathology. We then performed in vitro cell cultures of PBMCs from HD or TAK supplemented with Ruxolitinib (JAK1/2 inhibitor) or PBS. We observed by FC that JAKinibs significantly induced in TAK CD4+ and CD8+ T cells reduction of CD25 expression, decrease of Th1/Th17 pro-inflammatory cells and increase of Tregs.

Next, we followed by FC 3 TAK (refractory to conventional treatments) treated with JAKinibs. We also observed in their PBMCs a reduction of CD25 expression by CD4+ T cells, a decrease of Th1 and Th17 cells and an increase of Tregs, accompanied by an increase of the Tregs/Teffs ratio. JAKinibs also decreased C-Reactive Protein level, NIH score and co-administered steroids doses (present before JAKinibs introduction) in these 3 in vivo-treated TAK.

Conclusion: JAK/STAT signaling pathway is critical in the pathogenesis of TAK and JAKinibs may be promising in its treatment.

References:

- [1] F. Numano, M. Okawara, H. Inomata, Y. Kobayashi, The Lancet. 356, 1023–1025 (2000).
- [2] C. Comarmond et al., Circulation. 136, 1114–1122 (2017).
- [3] A. Mirouse et al., J. Autoimmun. 96, 35–39 (2019).
- [4] C. M. Weyand, J. J. Goronzy, Nat. Rev. Rheumatol. 9, 731–740 (2013).
- [5] C. M. Weyand et al., Clin. Immunol. 206, 33–41 (2019).
- [6] D. Saadoun et al., Arthritis Rheumatol. 67, 1353–1360 (2015).
- [7] T. Mirault, H. Guillet, E. Messas, Presse Médicale. 46, e189–e196 (2017).
- [8] D. P. Misra, S. Chaurasia, R. Misra, Autoimmune Dis. 2016, 1–8 (2016).

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SAT0247

PREDICTORS OF ADVERSE OUTCOMES IN DIFFUSE ALVEOLAR HEMORRHAGE OF IMMUNE AND NON-IMMUNE CAUSES: 12-YEAR EXPERIENCE FROM A UNIVERSITY HOSPITAL

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Background: Diffuse alveolar hemorrhage (DAH) is a rare, life-threatening condition that has either immune or non-immune etiologies. DAH caused by capillaritis can be immune-mediated (IM-DAH), e.g. anti-neutrophil cytoplasmic antibody (ANCA) vasculitis and systemic lupus erythematosus, but DAH may also result

from anticoagulation, heart failure, drugs or inhaled toxins. Since IM-DAH has specific therapies available, we hypothesized that patients with IM-DAH would have a better prognosis.

Objectives: We did a retrospective analysis of all DAH cases seen at our university hospital in the last 12 years to investigate the predictors of adverse outcomes.

Methods: Using Epic radiant and Agfa Radiology Information System databases, we queried electronic medical records of all patients admitted to our university between Jan 2007 to Jan 2019 who had the words “diffuse alveolar hemorrhage” in their chest x-ray report. We manually reviewed charts of all these patients to confirm true DAH. True DAH was defined as suspicion of DAH on chest x-ray plus inclusion of DAH on the discharge problem list. We did a detailed chart review of true DAH cases to extract information regarding demographics, baseline disease characteristics, physical/serology/imaging findings, treatment received, and outcomes. The outcomes of interest were death, intubation, shock, need for hemodialysis (HD), and red blood cell transfusions. We compared IM-DAH with non IM-DAH cases using descriptive statistics, t-test, and chi-squared tests. We used logistic regression models to assess the influence of baseline characteristics on outcomes. A p-value < 0.05 was considered statistically significant.

Results: There were 88 cases of DAH (M:F 54:34, median age 57) fulfilling inclusion criteria (Table 1). The non-immune etiology was diagnosed in 63%, while 36% were IM-DAH (18% ANCA associated, 9% SLE, 2% decompensated heart failure, the rest were others). No clear etiology for DAH was found in 37.5% cases. Death within 90 days of onset of DAH occurred in 37.5%, 5.6% had recurrent DAH, and 56.8% had sustained remission. Non-IM DAH cases had worse outcomes such as death and were less likely to experience sustained remission (Chi-squared = 19.1, p < 0.001), though IM-DAH were more likely to receive HD (Chi-squared = 7.5, p-value 0.01). Presence of extrapulmonary findings (e.g. nephritis) was a risk factor for adverse outcome, and was statistically significantly correlated with the amount of blood products received, need for HD and likelihood of death, which did not reach statistical significance. Shock and intubation were associated with a higher likelihood of death (p = 0.02 and p = 0.001, respectively).

Table 1. Comparison of Clinical Characteristics of Immune versus Non-Immune Cases of Diffuse Alveolar Hemorrhage

Variable	Immune cases (N = 32)	Non-immune cases (N = 56)	Statistical comparison
Age (years)	51.09	55.91	P = 0.196
%Female	43.8	35.7	P = 0.510
%presenting with hemoptysis	8 (25%)	14 (25%)	P = 0.101
%extrapulmonary findings	20 (62.5%)	1 (1.7%)	P = 6.9e ⁻¹⁰
pANCA positive	16 (50%)	2 (3.6%)	P = 0.0004
% on anticoagulation	9.4	2.5	P = 0.090
Mean Creatinine	2.38	1.89	P = 0.507
Mean hospital length of stay (days)	16.69	23.27	P = 0.139
Drop in Hemoglobin prior to DAH and day of DAH	0.24	1.17	P = 0.070
%Bronchoscopy-confirmed DAH	62.5	75.0	P = 0.694
Mean units of blood transfused	1.91	2.66	P = 0.448
%Need for hemodialysis	37.5	12.5	P = 0.010
%Shock (any kind)	21.9	32.1	P = 0.338
%Need for intubation	43.8	62.5	P = 0.122
%Death within 90 days	12.5	52.7	P = 0.0009

Conclusion: DAH, a life-threatening condition, has both immune and non-immune etiologies. Our 12-years, single-center, university hospital experience showed that IM-DAH has a better prognosis than non IM-DAH. Presence of extrapulmonary manifestations was associated with worse outcomes.

References:

- [1] Moo Suk Park. Diffuse Alveolar Hemorrhage. Tuberc Respir Dis (Seoul). 2013 Apr; 74(4): 151–162.
- [2] Nasser M, Cottin V. Alveolar Hemorrhage in Vasculitis (Primary and Secondary). Semin Respir Crit Care Med. 2018 Aug;39(4):482-493.

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SAT0248

PATTERNS OF DRUG TREATMENT FOR MAINTENANCE PHASE OF ANCA-ASSOCIATED VASCULITIS (AAV) IN REAL WORLD PRACTICE IN EUROPE – PROLONGED GLUCOCORTICOID USE IS COMMON AND VARIOUS TREATMENT REGIMES ARE USED

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	Maintenance start	6 months	12 months	18 months	36 months
Remission full/partial %	43 / 50	59 / 38	67 / 30	72 / 25	74 / 22
Receiving GC %	65	61	53	46	39
5mg or less	19	40	58	68	72
5-10mg	34	41	35	27	23
10-20 mg	25	16	6	4	4
More than 20mg	22	3	2	1	1
Receiving RTX %	21	21	19	17	14
RTX alone	10	10	10	11	8
RTX + GC	10	10	8	5	5
RTX + other + no GC	1	1	1	1	1

RTX maintenance schedules varied - 375mg/6 monthly 22%, 500mg/6 monthly 36%, 1000mg/6 monthly 31%, 375mg/12 monthly 1%, 500mg/12 monthly 4% and 100mg/12 monthly 3%. 32% had RTX initial regime adjustments on basis of B cell counts (44%), age (34%) or immunoglobulin levels (22%). Over 36 months 28% patients relapsed, 18% minor and 10% major (who then left follow up in this study). This led to greater GC use in the minor relapse patients at 36 months compared to those maintaining remission without relapse (48% vs 38%).

Background: Maintenance therapy following remission induction in ANCA associated vasculitis (AAV) is required to prevent relapse but patients are also still at risk from long term organ damage. This can be due to disease activity and also adverse events from therapy in particular high dose and prolonged use of glucocorticoids (GC).

Objectives: This retrospective study aimed to examine clinical outcomes and in particular the drug treatment used for maintenance in AAV patients managed in routine clinical practice in Europe.

Methods: 1478 AAV patients (France, Germany, Italy, Spain and UK) managed by 493 physicians (37% Rheumatologists) who completed induction therapy for organ or life threatening AAV and initiated maintenance therapy between 2014-16 were studied. Data were collected at the time maintenance was determined to begin by the physician and then at 6, 12, 18 and 36 months. 49% had granulomatosis with polyangiitis, mean age 54.2 years with 56% male. 49% had incident AAV and 51% were studied from a relapse. 70% received cyclophosphamide and GC and 30% received rituximab (RTX) and GC for remission induction therapy.

Results: Definition of maintenance start from the time of incidence/relapse and initial maintenance therapy varied between incident patients (mean time 4.7 months, GCs 66%, Azathioprine 38%, RTX 19%, Cyclophosphamide 11%) and relapsed patients (mean time 6.5 months *, GCs 63%, Azathioprine 30% *, RTX 24% *, Cyclophosphamide 20% *, p<0.05 vs incident). RTX use was notably higher in relapsing patients in Italy, Spain and UK compared to incident patients. Control of AAV activity varied over follow up and prolonged GC use was common even after 36 months including in RTX treated patients.

Conclusion: Maintenance therapy regimes used in clinical practice in Europe are variable including on basis of incident vs relapsing disease yet full remission is often not maintained. Many patients remain on GCs for long periods placing the patients at higher risk of GC related adverse events and organ damage. Even minor relapse increases the prolonged use of GCs. The high burden of prolonged GC use in AAV should be more clearly recognized and new therapeutic approaches explored.

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SAT0249 A PROBABILITY-BASED DIAGNOSTIC ALGORITHM FOR SUSPECTED GCA

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Table 1. US performance with PTPS

Category (n)	US GCA, n	Non-GCA, n	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence (%)	Accuracy (%)
HC (31)	+	24	1	24/27 (89)	3/4 (75)	24/25 (96)	3/6 (50)	27/31 (87)
IC (65)	-	3	3	30/30 (100)	35/35 (100)	30/30 (100)	35/35 (100)	30/65 (46)
LC (78)	+	0	35	0/0 (undefined)	77/78 (99)	0/1 (0)	77/77 (100)	0/78 (0)
Total (174)	+	54	2	54/57 (95)	115/117 (98)	54/56 (96)	115/118 (97)	57/174 (33)
	-	3	115					

Abbreviations: GCA, Giant cell arteritis; NPV, Negative predictive value; PPV, Positive predictive value; US, Ultrasound

Background: Clinical presentation of GCA is protean. It is vital to make a secure diagnosis, exclude mimics urgently and avoid inappropriate steroids to minimise side effects. Fast track GCA clinics (FTC) provide rapid specialist assessment with temporal and axillary US (1). EULAR recommendations support US as first-choice test. A pre-test probability score (PTPS) stratifies patients to low (LC), intermediate (IC) and high-risk (HC) categories.

Objectives: To validate a diagnostic GCA algorithm based on stratification by PTPS, with sequential US and additional tests (AT), if necessary

Methods: For the algorithm (Figure) retrospective data was extracted from case records of cases seen in 2019. PTPS overall showed median (Q2) score of 9.75th percentile (Q3) score 12. Based on this and reported cut-off 9.5 (2) we classified LC as PTPS <9, IC 9-12 and HC >12 (Graph). GCA diagnosis was by modified GACTA including US (Halo), CRP > 5 mg/L and AT if necessary. The algorithm performance was assessed overall and in individual categories.

Results: Of 187 consecutive cases, 13 were excluded for incomplete data (tertiary referrals). In remaining 174, GCA confirmed 33%, mean age 72.4 years, 69% females, 45% LC, 35% IC, and 20% HC. 130 (75%) had US whereas 44 did not (41 LC, 3 IC) (Figure)

In HC, 25/31 (81%) were US +ve, 19 treated as GCA without AT, 6 with AT (Table 2). Of 6 US -ve 3 had GCA confirmed by AT (PET-CT 2, TAB 1). US in HC showed sensitivity 89%, specificity 75%, accuracy 87%, GCA prevalence 87%, mean CRP 65.52 (SEM+/- 8.67).

In LC, 38 (49%) were US -ve, of whom 5 had AT. US not done on 39 (50%) for either PTPS very low or urgent alternative diagnosis. 1 went on to AT. 1 was US positive and had GCA excluded with AT. US in LC showed specificity 99%, sensitivity 0/0 (undefined), accuracy 99%, GCA prevalence 0%, mean CRP 21.79 (SEM+/- 3.80)

Graph-1: Categories according to the probability score