编号：YY001-20221205001

标题：Adeno-associated virus vector-mediated gene therapy for the treatment of ovarian cancer: a literature review

简介：Background and objective: The adeno-associated virus (AAV) is a member of the Parvoviridae family and has emerged as one of the most popular and promising approaches for gene therapy due to its low toxicity, low immunogenicity, and excellent safety after optimization. Advances in gene therapy methods have allowed novel treatments such as using AAV to knock out or repair target genes. AAV-mediated gene therapy has been used in numerous tumor studies, including lymphatic metastasis of prostate cancer, liver cancer, and renal cell carcinoma in mice. Ovarian cancer is an extremely aggressive malignancy which is prone to recurrence, and AAV vector-based gene therapy may be a potential treatment strategy. Methods: Herein, we reviewed the current research to provide an update on the role of AAV-mediated gene therapy in tumor research, especially in ovarian cancer. To find recent developments in pertinent research, we examined the PubMed database. Key content and findings: AAV vectors may produce steady and effective gene expression without becoming harmful, making it a viable gene delivery technique. AAV-based gene therapy products have been widely used in preclinical research and some have achieved marketing approval. Conclusions: Due to its affinity for various organs, reliable integration, and long-lasting expression, certain AAV serotypes have been widely used in gene therapy. However, there are also some challenges. Extensive research on the role of AAV in disease and gene therapy has shown great potential. Herein, we examined the literature to better understand the function of the AAV in tumor research, particularly in ovarian cancer research.

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编号：YY001-20221205002

标题：Co-transduction of dual-adeno-associated virus vectors in the neonatal and adult mouse utricles

简介：Adeno-associated virus (AAV)-mediated gene transfer is an efficient method of gene over-expression in the vestibular end organs. However, AAV has limited usefulness for delivering a large gene, or multiple genes, due to its small packaging capacity (< 5 kb). Co-transduction of dual-AAV vectors can be used to increase the packaging capacity for gene delivery to various organs and tissues. However, its usefulness has not been well validated in the vestibular sensory epithelium. In the present study, we characterized the co-transduction of dual-AAV vectors in mouse utricles following inoculation of two AAV-serotype inner ear (AAV-ie) vectors via canalostomy. Firstly, co-transduction efficiencies were compared between dual-AAV-ie vectors using two different promoters: cytomegalovirus (CMV) and CMV early enhancer/chicken β-actin (CAG). In the group of dual AAV-ie-CAG vectors, the co-transduction rates for striolar hair cells (HCs), extrastriolar HCs, striolar supporting cells (SCs), and extrastriolar SCs were 23.14 ± 2.25%, 27.05 ± 2.10%, 57.65 ± 7.21%, and 60.33 ± 5.69%, respectively. The co-transduction rates in the group of dual AAV-ie-CMV vectors were comparable to those in the dual AAV-ie-CAG group. Next, we examined the co-transduction of dual-AAV-ie-CAG vectors in the utricles of neonatal mice and damaged adult mice. In the neonatal mice, co-transduction rates were 52.88 ± 3.11% and 44.93 ± 2.06% in the striolar and extrastriolar HCs, respectively, which were significantly higher than those in adult mice. In the Pou4f3+/DTR mice, following diphtheria toxin administration, which eliminated most HCs and spared the SCs, the co-transduction rate of SCs was not significantly

different to that of normal utricles. Transgene expression persisted for up to 3 months in the adult mice. Furthermore, sequential administration of two AAV-ie-CAG vectors at an interval of 1 week resulted in a higher co-transduction rate in HCs than concurrent delivery. The auditory brainstem responses and swim tests did not reveal any disruption of auditory or vestibular function after co-transduction with dual-AAV-ie vectors. In conclusion, dual-AAV-ie vectors allow efficient co-transduction in the vestibular sensory epithelium and facilitate the delivery of large or multiple genes for vestibular gene therapy.

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编号：YY001-20221205003

标题：Utility of interval kidney biopsy in ANCA-associated vasculitis

简介：Objectives: ANCA-associated vasculitis (AAV) is a rare autoimmune disorder that commonly involves the kidney. Early identification of kidney involvement, assessing treatment-response and predicting outcome are important clinical challenges. Here, we assessed the potential utility of interval kidney biopsy in AAV. Methods: In a tertiary referral centre with a dedicated vasculitis service, we identified patients with AAV who had undergone interval kidney biopsy, defined as a repeat kidney biopsy (following an initial biopsy showing active AAV) undertaken to determine the histological response in the kidney following induction immunosuppression. We analysed biochemical, histological and outcome data, including times to kidney failure and death for all patients. Results: We identified 57 patients with AAV who underwent at least one interval kidney biopsy (59 interval biopsies in total; median time to interval biopsy ~130 days). Of the 59 interval biopsies performed, 24 (41%) patients had clinically suspected active disease at time of biopsy which was confirmed histologically in only 42% of cases; 35 (59%) patients were in clinical disease-remission, and this was correct in 97% of cases. The clinician's impression was incorrect in one in four patients. Hematuria at interval biopsy did not correlate with histological activity. Interval biopsy showed fewer acute lesions and more chronic damage compared with initial biopsy and led to immunosuppressive treatment-change in 75% (44/59) of patients. Clinical risk prediction tools tended to operate better using interval biopsy data. Conclusion: Interval kidney biopsy is useful for determining treatment-response and subsequent disease management in AAV. It may provide better prognostic information than initial kidney biopsy and should be considered for inclusion into future clinical trials and treatment protocols for patients with AAV.

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编号：YY001-20221205004

标题：CX3CL1-induced CD16+ monocytes extravasation in myeloperoxidase-ANCA-associated vasculitis correlates with renal damage

简介：Background: Monocytes are involved in the pathogenesis of ANCA-associated vasculitis (AAV). Monocyte/macrophages are the dominant infiltrating cells in the glomeruli of patients with myeloperoxidase-AAV (MPO-AAV). However, how human monocyte subsets extravasate to the kidney in MPO-AAV with renal damage is unclear. Methods: 30 MPO-AAV patients with renal damage and 22 healthy controls were enrolled in this study. Monocyte subsets and monocyte-related chemokines in the blood and kidneys of MPO-AAV patients were detected. The chemoattractant activity of the CX3CL1-CX3CR1 axis on CD16+ monocytes was observed. The

effect of MPO-ANCA on the migration of CD16+ monocytes to human glomerular endothelial cells (HGECs) was detected by flow cytometry and transwell migration assay. Results: Compared with controls, CD16+ monocytes were significantly decreased in the blood and increased in the glomeruli of MPO-AAV patients with renal damage. The level of CX3CL1, but not CCL2, was significantly increased in the plasma of MPO-AAV patients. CX3CL1 co-localized with glomerular endothelial cells in MPO-AAV patients with renal damage. Moreover, we initially found that MPO-ANCA promotes an increase of the chemokine CX3CL1 on HGECs, imposing recruitment on CD16+ monocytes. Finally, the percentage of CD16+ monocytes in the blood was found to be positively correlated with estimated glomerular filtration rate (eGFR) and negatively correlated with urinary protein creatinine ratio in MPO-AAV patients with renal damage. Furthermore, the urinary protein creatinine ratio was positively correlated with the infiltrating of CD14+ and CD16+ cells in the kidneys. Conclusion: Enhanced extravasation of CD16+ monocytes to the kidney via the CX3CL1-CX3CR1 axis may be involved in renal damage in MPO-AAV.

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编号：YY001-20221205005

标题：Neutrophil Extracellular Traps in ANCA-Associated Vasculitis and Interstitial Lung Disease: A Scoping Review

简介：Background: Deregulated neutrophil extracellular traps (NETs) formation is implicated in various diseases, including ANCA-associated vasculitis and pulmonary fibrosis (PF). Lung involvement is frequent in AAV, and interstitial lung diseases (ILDs) are strongly related to MPO-ANCA positivity and mainly reported in microscopic polyangiitis. The association between AAV and ILD is a strong indicator of poor prognosis and limited survival. Neutrophils, ANCA and NET interplay in PF development in AAV. This study aimed to review the literature concerning the implications of NET in lung fibrogenesis specifically focused on AAV associated with ILD, and the potential of NET as a theranostic marker. Methods: Through scoping review methodology, we used a descriptive thematic analysis to understand the pathogenic role of NETs in patients with AAV and pulmonary fibrosis and their further role as a theranostic marker of this disease. Results: The implications of NET in the pathogenesis of AAV and ILD, as well as an association between these two diseases, have been identified, but the underlying pathophysiological mechanisms are still unknown. The pharmacological or genetic inhibition of NET release reduces disease severity in multiple inflammatory disease models, indicating that NETs are potential therapeutic targets. In this regard, despite the lack of clinical data, we may hypothesise that an optimal management of AAV-ILD patients would require not only B-cells targeted therapy, but also NETs inhibition. Conclusion: Preliminary findings seem to display a lack of efficacy of traditional immunosuppressants, such as Rituximab, in this subset of patients, while to date no patients suffering from a definite ILD have been enrolled in clinical trials. Further insights would be provided by their employment, as a combination treatment, in common clinical practice. Although we can imagine that the inhibition of NETs in patients with AAV-ILD could reduce severity and mortality, we still lack the scientific basis that could improve our understanding of the disease from a molecular point of view.

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编号：YY001-20221205006

标题：Infection is associated with increased risk of MPO- but not PR3-ANCA-associated vasculitis

简介：Objectives: To determine whether development of ANCA-associated vasculitis (AAV) shows a relationship with a prior infection and if prior infection affects disease characteristics and outcome. Methods: All incident cases of AAV diagnosed in a defined region of Sweden from 2000 through 2016 were identified. For each case, 10 individuals from the general population, matched for age, sex and area of residence, were selected. Infections occurring in AAV patients and controls prior to the date of AAV diagnosis (index date for respective controls) were identified using an administrative database. Conditional logistic regression models were used to calculate odds ratios (OR) of developing AAV. Occurrence, clinical characteristics and outcome of AAV were analysed with respect to prior infection. Results: Two-hundred and seventy patients with AAV (48% female) and 2687 controls were included. Prior to diagnosis/index date, 146 (54%) AAV patients had been diagnosed with infection vs 1282 (48%) controls, with OR for AAV 1.57 (95% CI 1.18, 2.19) in those with infections of the upper respiratory tract and 1.68 (1.02, 2.77) in those with pneumonia. Difference from controls was significant in patients with MPO-ANCA 1.99 (95% CI 1.25, 3.1) but not in those with PR3-ANCA 1.0 (0.61, 1.52). Patients with prior infection showed higher disease activity at AAV diagnosis. No differences in disease characteristics, comorbidities or outcome in those with and without prior infections were observed. Conclusions: Respiratory tract infections are positively associated with development of MPO- but not PR3-ANCA vasculitis. Prior infection is associated with higher disease activity at AAV diagnosis.

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编号：YY001-20221205007

标题：A glance into the future of anti-neutrophil cytoplasmic antibody-associated vasculitis

简介：In the past decade, unprecedented progress has been made in understanding the pathogenesis, diagnosis, assessment, and treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs). International collaborations and input from several fields (e.g. immunology, rheumatology, and nephrology) have been critical for analyzing demographics, disease manifestations, and outcomes in clinical research studies. Such efforts opened new avenues for generating novel questions and rationale to design better clinical trials. In addition, clinical research has been a source of several biological discoveries and the starting point for knowledge seeking on the pathophysiology of AAV. Interestingly, the blending of clinical and basic research provides a platform for personalized medicine. Despite recent revisions on AAV classification, the incorporation of new findings on disease genetics and immunologic responses may soon result in changes in clinical practice. These advances will enhance the selection of more specific and targeted therapies. However, current unmet needs in the management of AAV are still sizable and heavily impact long-term survival. Especially, frequent relapses, damage accrual, and high morbidity contribute to poor outcomes. Finally, the lack of defined biomarkers for disease activity and the prognosis is a permanent challenge in AAV research. Our work provides an overview of the current state of the art in AAV literature and suggests bridges for the remaining knowledge gaps. It offers potential future directions for the clinical assessment, management, and research in the field toward a more personalized medicine approach.

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编号：YY001-20221205008

标题：Managing ANCA-associated vasculitis during COVID-19 pandemic: a single-center cross-sectional study

简介：The objective of the study is to report the outcomes of COVID-19 in ANCA-associated vasculitis (AAV) patients. This was a registry-based observational study conducted at a tertiary care center in north India. AAV patients with at least one follow-up visit between March 2020 and September 2021 were included. Demographic features, clinical manifestations, disease activity, and treatment details of underlying AAV were noted in all patients. Details of COVID-19 infection including severity, treatment, and outcomes were noted. Predictors of COVID-19 severity were determined using univariate analysis. A total of 33 (18.3%) out of 180 AAV patients contracted COVID-19 infection. Moderate COVID-19 infection was seen in 33.3% and severe or critical infection was seen in 36.3% of patients. Seventeen patients (51.5%) required supplemental oxygen therapy. Nine patients had active disease at the time of COVID-19 infection and three of them died due to COVID-19 infection. The risk of COVID-19 infection and its severity did not differ between patients receiving different immunosuppressants including rituximab induction. Hypothyroidism ($p = 0.046$) and ocular ($p = 0.038$) involvement due to AAV predicted the development of moderate to severe/critical COVID-19. Three (9.1%) patients died from COVID-19 and the rate of AAV flare after COVID-19 was similar to that in non-COVID-19 patients (15.3/100 person-year vs. 15.6/100 person-year, $p = 0.95$). Majority of the patients with AAV had moderate to severe or critical COVID-19 infection. The rate of death due to COVID-19 in AAV is higher than in general population. Use of standard remission induction regimens did not lead to increased risk of COVID-19 infection in our AAV cohort.

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编号：YY001-20221205009

标题：Interstitial nephritis without glomerulonephritis in ANCA-associated vasculitis: a case series and literature review

简介：The typical nephrological presentation of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is rapidly progressive glomerulonephritis. AAV-associated interstitial nephritis without apparent glomerular lesions was rare. We reported three local cases of AAV-associated interstitial nephritis without glomerulonephritis confirmed by renal biopsy. Then, a literature search was conducted in PubMed using free text words and MeSH terms related to "AAV and interstitial nephritis". Fifteen cases were included, and their demographics, clinical manifestations, laboratory data, renal pathological features, and treatment response were summarized. AAV-associated interstitial nephritis usually affects elderly patients. The common symptoms include fever, arthralgias, and edema. These patients were mostly MPO-ANCA positive. Pathological lesions in the kidney showed diffuse infiltration of inflammatory cells, edema, tubulitis, and fibrosis in the interstitial area. Various immunosuppressive treatments, including glucocorticoids, immunosuppressants, and rituximab, were used, and most of the patients achieved clinical remission. AAV-associated interstitial nephritis is rare but shows a characteristic clinical phenotype, serological results, and pathogenic lesions. Immunosuppressive therapy showed good efficacy in these patients.

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编号：YY001-20221205010

标题：ANCA-associated vasculitis following Johnson and Johnson COVID-19 vaccine

简介：Introduction: Antineutrophil cytoplasmic autoantibodies associated vasculitis (AAV) is characterized by antibodies against antigens in cytoplasmic granules of neutrophils and predominantly affects small vessels. AAV after COVID-19 mRNA vaccination has been reported. Case presentation: We report a rare case of AAV in a patient who presented with rapidly progressive glomerulonephritis (RPGN) after Johnson & Johnson COVID-19 vaccine administration. Discussion: The temporal causal association between autoimmune manifestations like AAV and COVID-19 vaccines can be explained by hypothesized mechanisms like molecular mimicry, defective neutrophilic apoptosis, polyclonal activation, and systemic proinflammatory cytokine response. These mechanisms are likely to trigger autoimmune responses in genetically susceptible individuals. Still there are many research going on to fill the research gap on the development of ANCA associated with COVID-19 vaccines. Conclusion: Increasing reports of rare adverse effects like AAV following COVID-19 vaccination warrants the further study and evaluation of immune responses induced by those vaccines. Considering the potential severity of COVID-19 and the rarity of the above-mentioned adverse effects, COVID-19 vaccination should not be withheld.

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编号：YY001-20221205011

标题：Natural Killer Cells in Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis - A Review of the Literature

简介：Anti-neutrophil cytoplasmic antibody (ANCA)- associated vasculitis (AAV) is a group of systemic autoimmune diseases characterized by inflammation of small- and medium-sized vessels. The three main types of AAV are granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). A growing number of studies focus on natural killer (NK) cells in AAV. NK cells are innate lymphoid cells with important roles in anti-viral and anti-tumor defense, but their roles in the pathogenesis of autoimmunity is less well established. In this review, we will present a summary of what is known about the number, phenotype and function of NK cells in patients with AAV. We review the literature on NK cells in the circulation of AAV patients, studies on tissue resident NK cells and how the treatment affects NK cells.

全文链接：https://pan.ckcest.cn/rcservice//doc?doc_id=108293

编号：YY001-20221205012

标题：Pulmonary involvement of ANCA-associated vasculitis in adult Chinese patients

简介：Objective: The aim of this study was to clarify the clinical characteristics and long-term outcomes of ANCA-associated vasculitis (AAV) patients with pulmonary involvement from a single Chinese cohort. Methods: Newly diagnosed AAV patients with pulmonary involvement, as defined by CT, were recruited from January 2010 to June 2020. Clinical data and CT images were collected retrospectively. Baseline CTs were evaluated and re-classified into four categories: interstitial lung disease (ILD), airway involvement (AI), alveolar hemorrhage (AH), and pulmonary granuloma (PG). Results: A total of 719 patients were newly diagnosed with AAV, 366 (50.9%) of whom combined with pulmonary involvement at baseline. Among the AAV cases with pulmonary

involvement, 55.7% (204/366) had ILD, 16.7% (61/366) had AI alone, 14.8% (54/366) had PG, and 12.8% (47/366) had AH alone. During follow-up of a median duration of 42.0 months, 66/366 (18.0%) patients died, mainly died from infections. Survival, relapse, and infection were all significantly different based on the radiological features. Specifically, the ILD group tends to have a poor long-term prognosis, the PG group is prone to relapse, and the AI group is apt to infection. The AH group has a high risk of both early infection and relapse, thus a poor short-term prognosis. Conclusion: AAV patients with diverse radiological features have different clinical characteristics and outcomes. Therefore, the intensity of immunosuppressive therapy must be carefully valued by considering the baseline CT findings among AAV patients with pulmonary involvement.

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编号：YY001-20221205013

标题：Protective α1-antitrypsin effects in autoimmune vasculitis are compromised by methionine oxidation

简介： BackgroundAntineutrophil cytoplasmic autoantibody-associated (ANCA-associated) vasculitidies (AAV) are life-threatening systemic autoimmune conditions. ANCAs directed against proteinase 3 (PR3) or myeloperoxidase (MPO) bind their cell surface-presented antigen, activate neutrophils, and cause vasculitis. An imbalance between PR3 and its major inhibitor α1-antitrypsin (AAT) was proposed to underlie PR3- but not MPO-AAV. We measured AAT and PR3 in healthy individuals and patients with AAV and studied protective AAT effects pertaining to PR3- and MPO-ANCA.MethodsPlasma and blood neutrophils were assessed for PR3 and AAT. WT, mutant, and oxidation-resistant AAT species were produced to characterize AAT-PR3 interactions by flow cytometry, immunoblotting, fluorescence resonance energy transfer assays, and surface plasmon resonance measurements. Neutrophil activation was measured using the ferricytochrome C assay and AAT methionine-oxidation by Parallel Reaction Monitoring.ResultsWe found significantly increased PR3 and AAT pools in patients with both PR3- and MPO-AAV; however, only in PR3-AAV did the PR3 pool correlate with the ANCA titer, inflammatory response, and disease severity. Mechanistically, AAT prevented PR3 from binding to CD177, thereby reducing neutrophil surface antigen for ligation by PR3-ANCA. Active patients with PR3-AAV showed critical methionine-oxidation in plasma AAT that was recapitulated by ANCA-activated neutrophils. The protective PR3-related AAT effects were compromised by methionine-oxidation in the AAT reactive center loop but preserved when 2 critical methionines were substituted with valine and leucine.ConclusionPathogenic differences between PR3- and MPO-AAV are related to AAT regulation of membrane-PR3, attenuating neutrophil activation by PR3-ANCA rather than MPO-ANCA. Oxidation-resistant AAT could serve as adjunctive therapy in PR3-AAV.FUNDINGThis work was supported by KE 576/10-1 from the Deutsche Forschungsgemeinschaft, SCHR 771/8-1 from the Deutsche Forschungsgemeinschaft, grant 394046635 - SFB 1365 from the Deutsche Forschungsgemeinschaft, and ECRC grants.

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编号：YY001-20221205014

标题：High burden of disease in patients with ANCA-associated vasculitis : A claims data study in Germany

简介： Background & objectives: Antineutrophil cytoplasmic antibody (ANCA)-associated

vasculitis (AAV) represents a group of rare chronic autoimmune diseases characterized by recurrent systemic inflammation provoking multiple morbidities. AAV patients suffer from various organ manifestations and treatment-related severe adverse effects. This retrospective study investigated the concrete burden of AAV disease on patients in Germany. Methods: Based on anonymized longitudinal German statutory health insurance (SHI) claims data from the years 2011-2016, a representative cohort of approximately 3 million insured persons was used to identify patients with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), and selected clinical aspects were systematically assessed. Results: The most frequent concomitant morbidities of GPA and MPA were renal and respiratory disorders. Severe renal involvement occurred in 11.6% of GPA and 24.3% of MPA patients within 15 quarters of diagnosis. Severe infections developed in one third of AAV patients within the first three quarters post-diagnosis. The annual rate of major relapses was 5-8%. AAV patients with renal impairment or infections showed increased annual mortality rates of 14.4 and 5.6%, respectively. Conclusion: Based on this analysis of German health care data, disease-specific assumptions regarding the burden on AAV patients were confirmed and concretized for the German context. AAV patients suffer from a high burden of morbidity, including multiple disease manifestations, relapses, and severe complications due to AAV treatment.

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编号：YY001-20221205015

标题：The association between ambient UVB dose and ANCA-associated vasculitis relapse and onset

简介：Background: The aetiology of ANCA-associated vasculitis (AAV) and triggers of relapse are poorly understood. Vitamin D (vitD) is an important immunomodulator, potentially responsible for the observed latitudinal differences between granulomatous and non-granulomatous AAV phenotypes. A narrow ultraviolet B spectrum induces vitD synthesis (vitD-UVB) via the skin. We hypothesised that prolonged periods of low ambient UVB (and by extension vitD deficiency) are associated with the granulomatous form of the disease and an increased risk of AAV relapse. Methods: Patients with AAV recruited to the Irish Rare Kidney Disease (RKD) (n = 439) and UKIVAS (n = 1961) registries were studied. Exposure variables comprised latitude and measures of ambient vitD-UVB, including cumulative weighted UVB dose (CW-D-UVB), a well-validated vitD proxy. An n-of-1 study design was used to examine the relapse risk using only the RKD dataset. Multi-level models and logistic regression were used to examine the effect of predictors on AAV relapse risk, phenotype and serotype. Results: Residential latitude was positively correlated (OR 1.41, 95% CI 1.14-1.74, p = 0.002) and average vitD-UVB negatively correlated (0.82, 0.70-0.99, p = 0.04) with relapse risk, with a stronger effect when restricting to winter measurements (0.71, 0.57-0.89, p = 0.002). However, these associations were not restricted to granulomatous phenotypes. We observed no clear relationship between latitude, vitD-UVB or CW-D-UVB and AAV phenotype or serotype. Conclusion: Our findings suggest that low winter ambient UVB and prolonged vitD status contribute to AAV relapse risk across all phenotypes. However, the development of a granulomatous phenotype does not appear to be directly vitD-mediated. Further research is needed to determine whether sufficient vitD status would reduce relapse propensity in AAV.

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