Other orphan diseases

AB0756

IMMUNE-MEDIATED BASIS FOR A PHASE 2A CLINICAL STUDY COMPARING RILZABRUTINIB VS GLUCOCORTICOCIDS IN RITUXIMAB-REFRACTORY PATIENTS WITH IGG4-RELATED DISEASE

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Background: IgG4-related disease (IgG4-RD) is an immune-mediated disorder causing fibro-inflammatory lesions. Although the cause remains unknown, it may be driven by interactions between B lymphocytes and CD4+ cytotoxic and regulatory T cells and is characterized by an increase in short-lived plasmablasts, circulating antibodies, and macrophages. Standard therapy mainly includes glucocorticoids (GC), limited by toxicity with long-term use (> 6 mo), and to a lesser extent, immunosuppressives (eg, rituximab). Bruton tyrosine kinase (BTK) plays an important role in the activation of multiple immune effector cells such as B cells, mast cells, eosinophils, basophils, monocytes/macrophages, and neutrophils. Dysregulation of the activation of these immune cells results in autoimmune inflammation, tissue damage, and development of fibrosis. Rilzabrutinib is a highly selective oral BTK inhibitor that targets multiple pathways of innate and adaptive immunity (with direct effects on B-cell and FcR pathways) and has the potential to inhibit antigen presentation to autoreactive T cells.

Objectives: To provide the biological rationale for rilzabrutinib in IgG4-RD.

Methods: Rilzabrutinib has been evaluated in biochemical, *in vitro* studies, and *in vivo* models of inflammatory diseases. Additional support is provided by the phase 2 trial for oral rilzabrutinib in patients with pemphigus vulgaris and the phase 2 trial for oral rilzabrutinib in patients with immune thrombocytopenia (ITP). **Results:** Rilzabrutinib inhibited the activity of BTK and B-cell receptor in B cells (IC₅₀ 5-123 nM) and Fc gamma receptor in IgG/Fc gamma receptor-stimulated monocytes (IC₅₀ 56 nM) and blocked IgG- and IgM-mediated antibody production in enriched B cells when stimulated in T-cell dependent (anti-CD40+IL-21) and T-cell independent (TLR-9/CpG and TNP-LPS) pathways. The impact of rilzabrutinib on innate cell pathways was further confirmed by significant dose-dependent inhibition of macrophage and neutrophil-driven passive rat Arthus reaction ($P < 0.01$ vs vehicle) and antibody-induced murine ITP ($P < 0.05$ vs vehicle). In a 12-week phase 2 pemphigus vulgaris trial, 54% of patients achieved the primary endpoint, control of disease activity (CDA) on low-dose corticosteroids by week 4, and 73% achieved it by week 12. In the phase 2 trial of ITP patients (median 6 prior therapies), rilzabrutinib 400mg bid showed rapid and sustained improvement in platelet counts and only grade 1/2-related adverse events¹. In responders, platelet counts increased as early as day 8, potentially due to innate immune mechanisms. Collectively, results in both B and innate immune cells provide an initial basis for evaluating rilzabrutinib in IgG4-RD. The ongoing phase 2a study (NCT04520451) is investigating rilzabrutinib 400mg bid (+tapered GC) vs GC control (3:1) for 12 weeks in IgG4-RD patients refractory to rituximab. The primary objective is to evaluate the safety and ability of rilzabrutinib to induce GC-free remission at week 12. Coupled with known preclinical/clinical findings, mechanistic analyses in this ongoing IgG4-RD study will profile B and other immune cell effects pre-/post-rilzabrutinib dosing to enhance the clinical understanding of rilzabrutinib in IgG4-RD.

Conclusion: Studies of rilzabrutinib that show beneficial effects on both B-cell and innate cell pathways provide support for its therapeutic role in immune-mediated diseases and for targeting the underlying pathophysiological effects of IgG4-RD. Effective and safe therapies that rapidly induce and maintain clinical responses, while minimizing the need for continuous GC treatment, remain an unmet need for patients with IgG4-RD.

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ON THE ISSUE OF DIFFERENTIAL DIAGNOSIS OF PANNICULITIS

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Background: Diagnosis of panniculitis (Pn) is associated with significant difficulties due to the variety of etiological factors, which include panniculitis-like T-cell lymphoma (PLTCL) – a rare variant of non-Hodgkin lymphoma.

Objectives: to study clinical and laboratory features of PLTCL in rheumatology.

Methods: Over 8 years PLTCL was diagnosed in 10 patients (9 women and 1 man, average age 37.2 ± 7.4) who were referred to V.A. Nasonova Research Institute of Rheumatology with a diagnosis of erythema nodosum or panniculitis. In addition to general clinical study, serum concentrations of α-1 antitrypsin, amylase, lipase, ferritin, creatine phosphokinase, immunological parameters (ANF-Hep2, dsDNA, C3 and C4 complements, CRP, ANCA, Scl-70, antibodies to cardiolipins G and M) were determined, and positron emission tomography combined with computed tomography (PET-CT), histological and immunohistochemical examination (IHC) of the biopsy sample of skin with subcutaneous fat from the affected areas were performed.

Results: The clinical picture of PLTCL was characterized by generalized red-crimson moderately painful (VAS pain intensity 45mm) subcutaneous nodes on the upper limbs and trunk (100%), face (60%) and lower extremities (75%), without ulceration and oily fluid leakage. A "trembling saucer" symptom was evident in 75% of the observed cases. All patients had febrile fever. No enlargement of the lymph nodes of the liver and spleen was observed. The blood test revealed leukopenia (up to 2.0 × 10⁹ /l) in 50% of cases, an increase in ESR and CRP by three or more times in 100% of cases. The biochemical blood test demonstrated an increase in LDH activity by two or more times in all patients. PET-CT in 100% of cases revealed an intense accumulation of 18F-FDG in the nodes which correlated with a high proliferative activity index. The morphological picture resembled lobular panniculitis without vasculitis. Tumor lymphocytes had an immunophenotype of cytotoxic T-lymphocytes: CD3+, CD8+, granzyme B+. To confirm the tumor nature of the infiltrate the rearrangements of the T-cell receptor genes were studied. Glucocorticoid therapy (23.5 ± 9.6 mg/day) was ineffective which required polychemotherapy in most patients.

Conclusion: PLTCL presents a complex diagnostic task that requires a multidisciplinary approach to verify the diagnosis and treatment tactics.

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CLINICAL PROFILES DIFFER IN IGG4-RELATED DISEASE WITH AND WITHOUT ATOPY: A LARGE CASE-CONTROL STUDY IN CHINA

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Background: IgG4-related ophthalmic disease (IgG4-ROD) is one of the phenotypes of IgG4-related disease (IgG4-RD), and its lesions are mainly located in the ocular. Currently, there are few studies on IgG4-ROD and no study has compared the phenotypic differences between IgG4-ROD and non IgG4-ROD (nIgG4-ROD). Thus, it is difficult to establish the optimal treatment strategy for IgG4-ROD.

Objectives: The aim of this study was to identify the disparities between the two groups and to clarify the risk factors for IgG4-ROD relapse.

Methods: The IgG4-RD patients diagnosed at Peking University People's Hospital between January 2009 and January 2020 were recruited in this study. Patients were divided into IgG4-ROD and nIgG4-ROD group according to the ophthalmic involvement. Demographic, clinical and laboratory data of two groups were collected and compared. Cox regression analysis was used to identify the independent risk factors for IgG4-ROD relapse.

Results: Two hundred and fifty-five cases of IgG4-ROD were identified in 434 IgG4-RD patients in this study. IgG4-ROD group had almost equal sex ratio (male to female 0.96:1 vs 2.14:1, $P<0.001$), younger age of disease onset (51.1 ± 13.2 vs 55.5 ± 13.5 , $P<0.001$) and diagnosis (54.4 ± 12.6 vs 56.9 ± 13.4 , $P=0.054$) comparing with nlG4-ROD patients. As compared to nlG4-ROD group, higher percentage of IgG4-ROD patients met the 2019 American College of Rheumatology/European League Against Rheumatism classification criteria (AECC) for IgG4-RD (89.4% vs 64.8%, $P<0.001$), moreover, IgG4-ROD patients had higher AECC scores (37.0 ± 12.9 vs 27.2 ± 14.0 , $P<0.001$) and IgG4-RD responder index (11.4 ± 6.0 vs 10.2 ± 6.3 , $P=0.045$). Allergic diseases (65.5% vs 26.3%, $P<0.001$) and multiorgan involvement [6(4-7) vs 3(2-5), $P<0.001$] were more common in IgG4-ROD group. IgG4-ROD was frequently associated with salivary gland (92.5% vs 45.3%, $P<0.01$), paranasal sinuses (38.8% vs 12.8%, $P<0.01$), lung (47.8% vs 32.4%, $P<0.01$) and lymph node (64.3% vs 46.4%, $P<0.01$) involvement, while retroperitoneal fibrosis (7.1% vs 21.2%, $P<0.01$) and biliary system lesions (25.1% vs 35.2%, $P<0.05$) were more common in nlG4-ROD. IgG4-ROD patients had higher serum IgG4 levels [$983(409-1838)$ vs $523(225-1370)$, $P<0.001$], IgG4/IgG ratio [$0.529(0.272-0.879)$ vs $0.294(0.143-0.629)$, $P<0.001$], IgE levels [$339.7(160.8-847.6)$ vs $259.4(83.1-653.3)$, $P=0.022$] and lower CRP levels [$2.24(1.00-4.70)$ vs $3.05(1.26-12.45)$, $P=0.004$]. The initial glucocorticoid plus immunosuppressant was a protective factor for IgG4-ROD relapse (HR 0.279, 95%CI 0.165-0.470, $P<0.001$), and IgG4-ROD patients treated with initial glucocorticoid plus immunosuppressant had longer relapse-free survival time than patients treated with initial glucocorticoid monotherapy (43 vs 17, $P<0.001$).

Conclusion: IgG4-ROD patients had distinctive clinical features compared with nlG4-ROD patients. The initial glucocorticoid plus immunosuppressant was a protective factor for IgG4-ROD relapse, which could prolong the relapse-free survival time of IgG4-ROD patients. These findings may have important implications for understanding and management of IgG4-ROD.

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AB0759

INDEX OF COMORBIDITY IN PATIENTS WITH LOBULAR PANNICULITIS-LIPODERMATOSCLEROSIS

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Background: Early diagnosis of comorbid burden and treatment of rheumatological patients, especially panniculitis (Pn), is a complex problem, the solution of which lies in an interdisciplinary approach and the development of a general algorithm for managing patients.

Objectives: To study the structure and frequency of comorbid conditions in patients with Pn-lipodermatosclerosis (LDS).

Methods: We examined 53 patients (3 men and 50 women aged 18 to 80) with verified LDS, who were observed at the V.A. Nasonova Research Institute of Rheumatology for ten years on average. The duration of the disease varied from 2 weeks to 20 years. Clinical, laboratory and instrumental examination of patients was carried out twice a year. Clinical examination was carried out to determine localization, prevalence, color and number of the affected areas of skin and subcutaneous fat (SCF), as well as pain intensity according to the Visual Analogue Scale (VAS). Laboratory and instrumental research included standard blood and urine tests, as well as computed tomography of the chest and Doppler ultrasound of the lower extremities. To assess the relationship between the presence of comorbid pathology and the course of LDS the patients were analyzed with the CIRS and Charlson indices.

Results: Most patients were overweight women (60.3%) with average weight of 91.5 ± 21.8 kg. Based on the duration of the disease we identified the main variants of the course of the disease: acute (up to 3 months), subacute (from 3 to 6 months), and chronic (more than 6 months). Skin lesions were associated with polyarthralgias ($n=18$) and/or myalgias ($n=12$), mainly in the area of the affected limb. In 16 patients an increase in the erythrocyte sedimentation rate was recorded on average up to 23.8 ± 7.8 mm/h. The level of C-reactive protein (CRP) was more than 3 times higher than normal in 7 patients, 4 of them had an acute course of LDS. In the study group 17 patients did not have comorbid diseases, 64.7% of them were under 50 years old with an acute course of LDS ($p=0.02$). Concomitant pathology was detected in 68% of patients mainly with chronic LDS. In 67.9% of cases it was presented by chronic venous insufficiency (CVI), in 60.3% – by exogenous constitutional obesity, in 45.2% – by rheumatic diseases (75% of these patients had osteoarthritis, 17% – rheumatoid arthritis, 8% – antiphospholipid syndrome) and in 39.6% – arterial hypertension. Most patients had one concomitant disease, almost a fifth of patients had two concomitant diseases. The proportion of patients with three comorbid diseases was

11.1%, four comorbid diseases – 8.3% and five comorbid diseases – 5.5%. When assessing the Charlson index, 10-year survival rates over 90% (index values from 0 to 2 points) were registered in 66% of patients, from 53 to 77% (index values of 3-4) – in 26.4% and less than 21% (≥ 5 points) – in 7.5%. The comorbidity index correlated with the age of patients ($r = 0.8$; $p<0.05$). There was no correlation between the Charlson index and the duration of LDS ($r=0.3$; $p=0.2$). In patients older than 61 one or more comorbid conditions were recorded. The CIRS index for this group averaged 4.2 ± 0.3 points (range 0-10), in most patients (45.2%) the CIRS index did not exceed 5 points. An analysis of the relationship between the Charlson and the CIRS scales confirmed their significant correlation at the level of $r=0.5$, $p=0.0000001$.

Conclusion: In patients with LDS a high incidence of comorbid pathology was detected. The treatment of this variant of panniculitis requires an interdisciplinary approach and interaction between doctors of different specialties.

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HIGH SERUM IGA LEVELS HAVE LIMITED CLINICAL SIGNIFICANCE IN PATIENTS WITH IGG4-RELATED DISEASE DIAGNOSED BY EXPERTS

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Background: While the diagnostic and classification criteria for IgG4-related disease (IgG4-RD) have been recently developed [1-3], it is known that, without appropriate exclusions, some non-IgG4-RDs may meet these criteria. In particular, hyper IL-6 syndromes, including Castleman disease, can be misdiagnosed as IgG4-RD. Some clinical findings, including elevated serum levels of C-reactive protein (CRP) or IgA, have been suggested to be useful for differentiating hyper IL-6 syndromes from IgG4-RD [4]. However, since few clinical studies have focused on IgG4-RD with high serum IgA levels, its clinical significance has not been well known.

Objectives: This study aimed to clarify the clinical significance of high serum IgA levels in patients with IgG4-RD.

Methods: We retrospectively investigated the clinical features of 170 patients with IgG4-RD on the basis of the presence or absence of elevated serum IgA levels (>410 mg/dL) at the time of diagnosis. The diagnosis of IgG4-RD was made by experts on the basis of the fulfillment of the comprehensive diagnostic criteria and/or each organ-specific diagnostic criteria.

Results: Elevated serum IgA levels were observed in 18 patients (10.6%). In the patients with elevated serum IgA levels, serum CRP levels were higher (1.14 ± 1.18 vs. 0.31 ± 0.63 mg/dL, $p=0.003$) and the prevalence of relapse during the clinical course was lower (5.6% vs. 27.6%, $p=0.046$) than in those without elevated serum IgA levels. However, there were no significant differences in the other clinical features including the number of involved organs (2.4 ± 1.3 vs. 2.8 ± 1.6 , $p=0.443$) and inclusion scores of the ACR/EULAR classification criteria (32 ± 14 vs. 36 ± 17 , $p=0.374$). To evaluate the influence of serum IgA elevation on relapse, we performed Cox regression analysis, which showed that the elevated serum IgA levels had no significant association with lower incidence of relapse but a tendency of it (hazard ratio 0.997, 95% confidence interval 0.994-1.000, $p=0.055$) during the clinical course. In addition, a prompt improvement in the IgG4-RD responder index [5] during the clinical course was seen in the patients with serum IgA elevation, suggesting a similar good response to glucocorticoids as in those without it.

Conclusion: The findings of the present study suggest that IgG4-RD patients with high serum IgA levels can be diagnosed and treated in the same way as those without it, although they may be characterized by mild serum CRP elevation.

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