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.