THU0560

DISTINCTIVE IMAGING FEATURES BETWEEN IGG4-RELATED OPHTHALMIC DISEASE AND GRAVES' ORBITOPATHY: A COMPARATIVE STUDY

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Background: IgG4-related ophthalmic disease (IgG4-ROD) may present as a cause of orbital myositis leading to proptosis and diplopia. This clinical scenario can be mistakenly diagnosed as Graves' orbitopathy (GO), preventing a timely and adequately treatment.

Objectives: To elucidate if there are specific radiological features that might differentiate between IgG4-ROD and GO by imaging.

Methods: We included 19 patients with diagnosis of IgG4-related disease (IgG4-RD) according to the Comprehensive Diagnostic Criteria for IgG4-RD, who regularly attended a tertiary referral center in Mexico City. All the patients had ophthalmic involvement and available computed tomography (CT) and/or magnetic resonance imaging (MRI) of the orbits. We also included 32 patients with GO with available CT and/or MRI of the orbits. Imaging studies were evaluated by a blinded head and neck radiologist for the following features: exophthalmos, extraocular muscles (EOM) size and morphology, lacrimal gland enlargement, orbital fat involvement, stretching of the optic nerve (ON), ON sheath thickening and orbital bone changes.

Results: Both groups were similar in age (49.1±15.8 vs. 51.6±14.7, p=0.58) and gender (men 58.9% vs. 40.6%, p=0.23). In addition to ophthalmic involvement, 18 (94.7%) IgG4-RD patients had extra-ophthalmic involvement with a median number of organs involved of 7 (1-12), mainly submandibular glands (73.7%), lymph nodes (68.4%), parotid glands (63.2%) and pancreas (47.4%). Three patients were misdiagnosed as GO before IgG4-RD diagnosis. Graves' disease was the underlying thyroid disorder in 28 (87.5%) GO patients, Hashimoto's thyroiditis in 2 (6.3%), papillary thyroid carcinoma in one (3.1%) and one patient was euthyroid with positive thyroid stimulating immunoglobulin. The prevalence of exophthalmos (78.9% vs. 93.8%), bilateral involvement (78.9% vs. 87.8%) and overall EOM involvement (47.4% vs. 68.8%) was similar between IgG4-ROD and GO groups. However, IgG4-ROD patients had a higher frequency of lacrimal gland involvement (73.7% vs. 10.7%, p=0.001) and a tendency for the lateral rectus to be the most frequently involved EOM (22.2% vs. 0%, p=0.07); conversely they had a lower prevalence for the inferior rectus to be the most frequently involved EOM (33.3% vs. 72.7%, p=0.04), orbital fat involvement (47.4% vs. 81.3%, p=0.01), ON stretching (57.9% vs. 87.5%, p=0.02) and orbital bone changes (0% vs. 25%, p=0.02). EOM bellies were involved in all the IgG4-ROD and GO cases, whereas EOM tendon involvement was present in 9% of GO and in none of the IgG4-ROD group. Patients with IgG4-ROD had more frequently the combination of lacrimal gland and lateral rectus (31.6% vs. 3.1%, p=0.008) and less frequently the combination EOM and orbital fat involvement (21.2% vs. 59.4%, p=0.008).

At the logistic regression analysis we found an association of lacrimal gland involvement (OR 64.4, 95% CI 6.8-609.5, p=0.001) with IgG4-ROD. In a second model including combined variables, the combination of lacrimal gland and lateral rectus involvement was associated with IgG4-ROD (OR 62.5, 95% CI 3.31-1000, P=0.006), whereas the presence of EOM and orbital fat involvement was protective (OR 0.05, 95% CI 0.006-0.48, p=0.009).

Conclusion: Imaging features may reliably differentiate between IgG4-ROD and GO. The presence of both lacrimal gland and lateral rectus enlargement must alert clinicians to consider IgG4-ROD diagnosis.

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CANAKINUMAB FOR THE TREATMENT OF ADULT ONSET STILL'S DISEASE TO ACHIEVE REDUCTION OF ARTHRITIC MANIFESTATION AT WEEK 12: AN INVESTIGATOR-INITIATED MULTI-CENTRE, PLACEBO-CONTROLLED STUDY (CONSIDER)

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Background: Inhibition of interleukin-1 (IL-1) represents a promising treatment option in adult-onset Still's disease (AOSD). Canakinumab (CAN) is approved for treatment of systemic juvenile idiopathic arthritis (sJIA) since 2013 and recently for AOSD in Europe. In sJIA, CAN has a proven marked impact on systemic and articular disease activity, but for AOSD RCT data is limited.

Objectives: Investigation of efficacy and safety of CAN in AOSD patients with joint involvement by means of a multi-centre, double-blinded, randomized, placebo controlled trial.

Methods: AOSD patients with joint involvement (tender and swollen joint count ≥ 4 each) were stratified by pre-treatment status with biologics and randomized in a ratio of 1:1 to CAN (4 mg/kg up to a maximum of 300 mg) or placebo (PBO) s.c. every 4wks. The primary endpoint was defined as the proportion of patients with a clinical-relevant reduction (≥ 1.2) in disease activity as measured by change in disease activity score (DAS28) at week 12. There were two major protocol violations: two PBO patients received blinded CAN at week 4. Therefore, a per-protocol (PP) analysis, which excluded data of these two patients, was performed.

Results: The study was prematurely stopped with 35 out of 68 planned patients enrolled due to approval of CAN for AOSD by EMA. At enrollment, mean DAS28 represented high disease activity for both: 5.4 in CAN (n=18) and 5.3 in PBO (n=17). In the intention-to-treat analysis, 12 (67%) CAN and 7 (41%) PBO patients met the primary endpoint. The 25.5% [95%CI: -10.3%; 55.9%] difference in the response rate did not achieve statistical significance (p=0.18). Using the PP analysis, the treatment difference for primary endpoint was 33.4% [95%CI: -10.3%; 55.9%, p=0.08]. We observed higher ACR50 (50% CAN vs. 6.7% PBO, p=0.009), ACR70 (28% CAN vs. 0% PBO, p=0.049) response rates, (PP analysis). Higher mean improvements in the CAN vs PBO group for DAS28(ESR and CRP), ESR, CRP, 66 swollen and 68 tender joint counts at week 12 were observed (PP analysis). There were 47 and 21 non-serious adverse events (AE) reported in CAN and PBO groups, respectively. Two CAN patients experienced an SAE (hepatotoxicity and patellofemoral pain syndrome).

Conclusion: Although the study was terminated prematurely and the primary endpoint did not achieve statistical significance, treatment of patients with active AOSD with CAN led to improvement of several outcome measures. In addition, safety profile was similar to that reported in sJIA and no unexpected safety issues were observed. This data support the treatment of AOSD patients with CAN.

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Table 1. Characteristics of 9 patients from 1 center

Patient	Age/ Sex	Tumor type	Checkpoint Inhibitor	Fulfilled EULAR/ACR Classification Criteria*	Unfulfilled Criteria	Atypical Features	Treatment
1	63 M	RCC	Nivolumab	No; 5 points	Acute phase reactants		Prednisone 40 mg; tocilizumab 162 mg q2 weeks
2	69 M	Melanoma	Ipilimumab/ nivolumab	Yes; 6 points		Sicca symptoms; ANA 1:1280, anti-SSA >8 IU	Prednisone 30 mg
3	79 M	Melanoma	Ipilimumab/ nivolumab	Yes; 7 points**		Sicca symptoms	Prednisone 20 mg
4	57 M	Melanoma	Pembrolizumab	No; 3 points	Acute phase reactants; RF 35 IU/ml; knee involvement		Prednisone 60 mg
5	60 M	Melanoma	Pembrolizumab	No; 3 points	RF 45 IU/ml; knee involvement		Prednisone 60 mg
6	66 M	Melanoma	Nivolumab	Yes; 5 points	Hand involvement		Prednisone 20 mg; MTX
7	69 F	RCC	Nivolumab	Yes; 5 points	Hand involvement		Prednisone 10 mg; tocilizumab 162 mg q2 weeks
8	66 M	RCC	Durvalumab; tremilimumab	Yes; 5 points	Hand involvement		Prednisone 20 mg
9	72 F	RCC	Avelumab	Yes; 4 points	Acute phase reactants; hand and knee involvement		Prednisone 20 mg

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PREVALENCE, UNDERLYING FACTORS AND DAMAGE ASSOCIATED WITH CHRONIC PERSISTENT INFLAMMATION IN PATIENTS WITH FMF

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Background: Familial Mediterranean Fever (FMF) is the most frequent auto-inflammatory disease characterized by recurrent, self-limiting attacks of fever, peritonitis, pleuritis, synovitis, myalgia, and erysipelas-like erythema (ELE). Attacks has a robust inflammatory response which completely normalize when attacks subside. However, substantial number of FMF patients possess chronic persistent inflammation even in between attacks. Clinical significance of persistent inflammation and its contribution to damage accrual are yet to be determined.

Objectives: We aimed to determine the prevalence and underlying factors of chronic persistent inflammation and its association with the domains of Auto-inflammatory disease damage index (ADDI) in a large cross-sectional multicenter cohort.

Methods: All patients recruited from FMF in Central Anatolia (FiCA) cohort, which is a duplication disabled, internal and externally controlled, cross-sectional, multicenter accessible web-based cohort. Demographic data, disease characteristic, attack features (ever presented) were meticulously questioned. Genotype data (if available) and laboratory features including inflammatory markers were recorded. FMF related damage scores was assessed by auto-inflammatory disease damage index (ADDI) which is recently validated. Patients were stratified according to their antecedent acute phase responses as having persistent inflammation (PI

group) or not, both groups compared in terms of disease characteristics, attack features, inflammatory comorbidities and damage domains.

Results: Study is comprised 970 adult patients (mean age 35.3±12.1, 61% female). 54 of them were excluded for their first inclusion. 15% of patients had persistent inflammation. PI group had significantly younger age of diagnosis, male dominance, homozygous M694V, more frequent attacks it the last year, more pleuritis, arthritis, myalgia and ELE and more severe disease according to ISSF than other patients (Table-1). Moreover, colchicine resistance and ADDI damage scores were remarkably higher in PI group.

In multi-variate analyzes colchicine resistance OR=2.71 [95%CI 1.38-5.35], ISSF OR=11.06 [95%CI 5.23-23.39], male gender OR= 2.38 [95%CI 1.51-3.76], homozygous M694V mutation OR= 2.31 [95%CI 1.41-3.78] and ELE OR= 1.72 [95%CI 1.04-2.857] found as independent predictors of persistent inflammation. PI group had more damage in multiple domains like joint restriction, musculoskeletal pain, proteinuria, amyloidosis, renal insufficiency and developmental delay. Same variables and persistent inflammation further analyzed in in terms of predicting the damage. Persistent inflammation found to be an independent predictor of proteinuria OR=2.02 [95%CI 1.05-3.90], amyloidosis OR=2.71 [95%CI, 1.34-5.48]), and renal insufficiency OR=4.36 [95%CI 1.84-10.32].

Conclusion: Persistent inflammation is relatively common in FMF patients particularly in those harboring M694V homozygous mutation and is associated with major complications of disease indicating poor prognosis.

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Table 1 Patients demographics and disease characteristics |

	Persistent inflammation (n=142)	Others (-) (n=784)	p
Age, years	35(12.1)	35 (12.1)	0.09
Female	74 (52.1%)	492 (62.8%)	0.017
Disease onset <20 years	128 (90.1%)	585 (74.6%)	<0.001
Age at FMF diagnosis, years	22.6 (14.2)	25.1 (13.0)	0.041
M694V/M694V*	91 (71.1%)	240 (36.8)	<0.001
Fever	116 (81.7%)	655 (83.5%)	0.708
Peritonitis	125 (88%)	723 (92.2%)	0.158
Pleuritis	84 (59.2%)	351 (44.8%)	0.001
Arthritis	93 (65.5%)	301 (38.4%)	<0.001
Myalgia	57 (40.1%)	138 (17.6%)	<0.001
Erysipelas like erythema	68 (47.9%)	170 (21.7%)	<0.001
Attack frequency in the last year	8.37 (9.9)	3.78 (5.3)	<0.001
ISSF			
Mild Disease	9 (6.3%)	440 (56.1%)	
Intermediate Disease	91 (64.1%)	325 (41.5%)	<0.001
Severe disease	42 (29.6%)	19 (2.4)	
Colchicine resistance	38 (26.8%)	38 (4.8%)	<0.001
ADDI	2.2 (2.5)	0.9 (1.2)	<0.001
Joint restriction	13 (9.2%)	14 (1.8%)	<0.001
Musculoskeletal pain	84 (59.2%)	364 (46.4%)	0.006
Proteinuria	27 (19%)	37 (4.7%)	<0.001
Amyloidosis	28 (19.7%)	27 (3.4)	<0.001
Renal Insufficiency	20 (14.1)	15 (1.9%)	<0.001
Developmental delay	5 (3.5%)	9 (1.1%)	0.049
Solenomegaly	21 (14.8%)	34 (4.3%)	<0.001

ISSF: international severity scoring system for FMF. ADDI: autoinflammatory disease damage index
*n=14 missing in PI, n=132 missing in others

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