THU0580

JOINT MANIFESTATIONS SECONDARY TO IMMUNOTHERAPY: CLINICAL CHARACTERISTICS AND EVOLUTION

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Background: Inhibitors of CTLA-4 and PD-1 have shown improvements in survival in multiple advanced cancers. Immune-mediated effects such as arthralgias and arthritis have been described, but their prevalence and characteristics have not been well defined.

Objectives: The objective of the study is to describe the prevalence of immunomediated joint manifestations (IJM), its characteristics and evolution in patients who received immunotherapy (nivolumab (NV), pembrolizumab (PB)) from January 1, 2016 to December 31, 2018 in our center.

Methods: Data collection was performed at through the RPT (Registre Pacients Tractats) database of the CatSalut, and the patients referred to the monographic medical office of inflammatory joint diseases of our center. In all cases, the variables: age, sex, neoplasia, drug, number of doses, were recorded. In patients with joint involvement: other autoimmune manifestations, joint affection prior to treatment, delay rheumatology derivation, joint affection type, swollen and tender joint counts, ESR, CRP, RF, ACPA, ANA, HLA B 27, Hb, leukocytes, neutrophils, lymphocytes, treatment and evolution, were recorded. The statistical analysis was carried out with the SPSS 15.0 computer package

Results: 106 patients received treatment (TTO) with immunotherapy (71 NV, 35 PB) for neoplasia (81 lung, 10 renal, 8 melanoma, 2 oropharynx). The mean age was 67.93 ± 10.7 years (21.7% women, 78.3% men). There were 11 events cataloged as IJM. The overall prevalence was 10.3% (5.6% NV, 14.3% PB). Patients with IJM received a greater number of doses (17.67 ± 9.3 vs 9.24 ± 10.1 p = 0.018). No patient with melanoma presented IJM. All IJM suspicions cases were assessed by a rheumatology. When studying their characteristics (Table 1), 3 patients were added from the database of the rheumatology service (14 cases). They received in a clinical trial BP29541 (rectal cancer), Atezolizumab (lung cancer) and Durvalumab (lung cancer). 42.9% of the patients presented inflammatory arthralgias (IAT) and 57.1% arthritis (AT). In reference to their previous history, 2 patients had a history of hyperuricemia and arthritis. One patient concomitantly presented lymphocytic colitis confirmed by biopsy. The delay time for assessment by rheumatology was 18.1 ± 22.1 days. Patients with AT were older (p = 0.014), had higher ESR (p = 0.047) than those with IAT. No differences were found in other variables (table1). With reference to the analytical study, 1 patient was RF +, 2 ANA + at mean titers (1/160-1/320), none ACPA or HLA B 27 +. After assessment by rheumatology, two patients with IAT were diagnosed with bone M1 and two AT were categorized as gouty arthritis. The rest of the IAT responded to NSAIDs, did not require corticosteroids and were resolved. 6 cases of AT received prednisone, 3 required treatment dose 1 mg/kg weight and subsequently MTX in 2 of them, with evolution to low disease activity at present. Only one patient met RA classification criteria.

Conclusion: The prevalence of IJM was higher than 10%, depending on the number of doses. Patients with arthritis had higher age and higher ESR. No patient presented ACPA and HLA B 27 +, so to include them in the initial analytical could be not necessary. In these patients, it is important the assessment by a rheumatologist to make a correct differential diagnosis, as well as establish referral circuits to avoid delay of care

	ARTHRITIS (AT)	ARTHRALGIA (IAT)	P value
Age	71 ± 6,0	59,3 ± 9,7	0,014
Swollen joints	3,63 ± 3,4	0	0,026
Painful joints	10,75 ± 15,7	10,0 ± 8,7	0,919
ESR	39,5 ± 25,3	9,0 ± 4,3	0,047
CRP (mg/dl)	15,6 ± 11,6	5,0 ± 8,8	0,156
Leukocytes (cel x 10 ³)	11,026,2 ± 3264,2	8,156 ± 3,357,6	0,134
Lymphocytes (cel x 10 ³)	1,696,2 ± 1042,8	1,836,6 ± 1,188,4	0,818
Neutrofilos (cel x 10 ³)	8263,7 ± 2,668	5,523,6 ± 3,531	0,123
Hb(mg/dl)	10,8 ± 2,1	12,1 ± 2,64	0,325

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BIOLOGICAL THERAPY IN NON ISCHAEMIC OPTIC NEURITIS ASSOCIATED TO IMMUNE-MEDIATED INFLAMMATORY DISEASES. MULTICENTER STUDY

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Background: Non ischaemic optic neuritis (NION) is a severe inflammation of the optic nerve that may lead to blindness. It can be primary or associated to immune mediated inflammatory diseases (IMIDs). The treatment of the NION is based on systemic corticosteroids and conventional immunosuppressive drugs.

Objectives: To assess the efficacy of the biological treatment in refractory NION to conventional treatment.

Methods: Multicenter study of 12 patients diagnosed with NION refractory to systemic corticosteroids and at least one conventional immunosuppressive drug. The main outcomes were visual acuity (VA) and optical coherence tomography (OCT) of the optic nerve and the ganglionar cells. Comparisons were made between baseline and the 1st week, 1st and 6th month and 1st year. (STATISTICA, StatSoft Inc. Tulsa, Oklahoma, USA).

Results: We studied 12 patients (19 affected eyes) (5 men/7 women); mean age of 29.8 ± 12.9 years. The underlying diseases were systemic lupus erythematosus (n=1), neuromyelitis optica (n=1), neuroretinitis (n=1), relapsing polychondritis (n=1), pars planitis (n=1), Behçet's disease (n=2) and idiopathic (n=5). Before biological treatment and besides oral corticosteroids, patients had received intravenous (IV) methylprednisolone boluses (n=9), cyclosporine A (n=1), cyclophosphamide (n=2), mycophenolate (n=2), hydroxychloroquine (n=1), methotrexate (n=8) and azathioprine (n=5). Biological treatment was based on rituximab (n=2) (2 IV, doses of 1 g/very 2 weeks and every 6 months), adalimumab (n=5) (40 mg/1-2 week), tocilizumab (n=4) (8 mg/kg/2-4 weeks) and infliximab (n=3) (5 mg/kg at 0, 2 and 6 week and then every 8 weeks). The characteristics of the 12 patients are shown in the TABLE.

After biological treatment we observed an improvement in the ocular parameters: VA [0.66±0.32 to 0.84±0.29; p= 0.03], OCT of the optic nerve [123.20±58.28 to 190.54±175.38; p= 0.11], and OCT of the ganglionar cells [369.55±137.37 to 270.67±23.21; p= 0.03] at one year. After a mean follow-up of 29.09 ± 19.23 months, there were no severe adverse effects.

Conclusion: Biologic therapy in NION idiopathic or associated to IMIDs, refractory to conventional treatment, seems to be effective.

Case	Sex/Age (years)	Underlying disease	Laterality	Immunosuppressive drugs before biological therapy	Biological therapy
1	Man/29	Idiopathic	Right	AZA	TCZ
2	Man/26	Idiopathic	Bilateral	AZA	TCZ
3	Man/21	Idiopathic	Bilateral	MTX, AZA	ADA
4	Woman/25	Behçet's disease	Right	MTX, CyA	ADA
5	Woman/39	Behçet's disease	Right	MTX, MMF	IFX
6	Woman/14	Neuroretinitis	Bilateral	MTX	ADA
7	Man/56	SLE	-	Hydroxychloroquine, MMF, CFM	RTX
8	Woman/43	Neuromyelitis optica	Bilateral	AZA	RTX
9	Man/43	Relapsing polychondritis	Bilateral	MTX, CyA	IFX, TCZ
10	Woman/24	Pars planitis	Bilateral	MTX, AZA	ADA
11	Woman/13	Idiopathic	Bilateral	MTX	ADA
12	Woman/25	Idiopathic	Bilateral	MTX	IFX, TCZ

ADA: adalimumab, AZA: azathioprine, CFM: cyclophosphamide, CyA: cyclosporine A, HCO: hydroxychloroquine, IFX: infliximab, MMF: mycophenolate, MTX: methotrexate, RTX: rituximab, SLE: systemic lupus erythematosus, TCZ: tocilizumab

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THE TNF RECEPTOR-ASSOCIATED PERIODIC SYNDROME (TRAPS): CLINICAL AND GENETIC CHARACTERIZATION OF A COHORT OF ADULTS DIAGNOSED OF TRAPS SYNDROME

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Background: Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is a disease that is included within of hereditary syndromes of periodic fever. It presents an autosomal dominant pattern of inheritance. It's due to mutations of TNFRSF1A gene. It is usually present in childhood although it can also appear in adulthood and it tends to cause high levels of acute phase reactants, fever, musculoskeletal symptoms (myalgias, arthralgias, arthritis), rash, abdominal pain, etc

Objectives: To describe the clinical characteristics and genetic variants of patients diagnosed with TRAPS syndrome in a cohort of patients with autoinflammatory syndromes with follow-up in a tertiary hospital from 2013 to the present

Methods: Retrospective descriptive study of adult patients diagnosed with autoinflammatory syndrome since 2013 (year of introduction of genetic tests in the hospital laboratory) until now. The data was obtained from the review of medical records. All patients with mutations in TNFRSF1A gene and clinically compatible with this diagnosis were reviewed

Results: Of a total of 44 adult patients diagnosed with hereditary syndromes of periodic fever (FMF, TRAPS, cryopyrinopathies, HIDS) and compatible genetic mutations (excluding polymorphisms), 13 (29.5%) presented mutations in the TNFRSF1A gene. Of those 13 patients, 9 (69.2%) were women. The most frequent mutations were the mutation in heterozygosis in exon 4 (p.R92Q) with 12 cases (92.3%) and one case (7.6%) with mutation in heterozygosis in exon 3 (p.P46L). The mean age at diagnosis was 27.92 years (IR 12-55 years). 5 patients showed simultaneous genetic variants in other genes related to autoinflammatory syndromes. Signs and/or symptoms were myalgia and elevation of acute-phase reactants with 12 patients (86%) followed by fever and joint symptoms (arthralgias and/or arthritis) with 11 patients (79%) were the most frequent. 2 patients (14%) had conjunctivitis. 9 patients (64%) presented cutaneous involvement. 2 cases (14%) presented lymphadenopathy. Regarding treatment, 5 patients (36%) had received treatment with biological therapy (anti-IL-1 or anti-TNF) and another 5 patients (36%) had used colchicine. The corticoids were used in 6 patients (43%)

Conclusion: The TRAPS syndrome is a clinical entity to consider when making a differential diagnosis in patients with suspected autoinflammatory syndrome, that present fever, acute phase reactants elevation, arthromyalgia and its confirmation diagnosis is with genetic test

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EXPERIENCE OF ANAKINRA AND CANAKINUMAB IN PATIENTS WITH COLCHICINE-RESISTANT FAMILIAL MEDITERRANEAN FEVER AND COMPLICATED WITH AMYLOIDOSIS

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Background: Familial Mediterranean Fever (FMF) is a hereditary auto-inflammatory disease characterized by recurrent fever and serosal inflammation (1). The goal of FMF treatment is to prevent the attacks and to minimize subclinical inflammation between attacks, and in attacks-free period. Colchicine is a major drug that sine qua non in the treatment of FMF. However, anti-interleukin-1 agents are recommended in colchicine resistant and/or intolerant FMF patients (2).

Objectives: The aim of this study is to evaluate the efficacy of anti-interleukin-1 (anti-IL-1) agents in 54 FMF patients with resistant/intolerant to colchicine or complicated with amyloidosis.

Methods: Between January 2014 and December 2018, fifty four patients who were diagnosed as FMF according to the criteria of Tel-Hashomer that following-up at Sivas Cumhuriyet University Medical Faculty, Rheumatology-Internal Medicine Department were included in to the study.

Results: 25 (46.3%) male and 29 (53.7%) female were included in the study. The median age of the patients was 29 (min:17-max: 60) years and the median age at diagnosis was 18 (min: 3-max: 46) years. Anakinra was used in 34 (63%) FMF patients (100 mg/day), and

canakinumab was used in 20 (37%) patients (150mg/8weeks). 37 cases were resistant to colchicine, 8 were intolerant to colchicine, 9 (20%) cases were complicated with amyloidosis. 8 patients had renal transplantation. MEFV gene mutations are shown in Table 1. Median duration of anti-IL-1 agent use was 12 months (min:2-max40). 5 patients were resistant to anakinra, 4 patients had side effects which anakinra related. After a median follow up 12 months overall clinical response was%95 (frequency of attacks <1/6months). Median proteinuria decreased from 3850 mg/day to median 1600 mg/day (p= 0.04) (Table 2). IL-6 treatment was started in 3 patients because of ineffectiveness of canakinumab. One pregnant patient was followed up with anakinra during pregnancy and there were no problems.

Conclusion: Anti-interleukin-1 agents can be used effectively and safely in the treatment of FMF patients. These agents are especially effective in the treatment of proteinuria due to amyloidosis. Large and long-lasting follow-up studies are needed to evaluate long-term effects of these drugs.

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Table 1. MEFV mutations in FMF patients

MEFV Mutations	n
M694V homozygus	20 (37%)
M694V heterozygous	8 (15%)
Compound mutation	14 (26%)
Other mutation	8 (15%)
No mutation	4 (8%)

Table 2. Laboratory Findings of the FMF patients treated with anti-IL-1 agents

	Pre-treatment (median)	Post-Treatment (median)	p
Number of attacks	>2/6month	<1/6month	p<0.05
ESR mm/h	33	8	p<0.05
CRP mg/dl	43	4.3	p<0.05
Proteinuria mg/day	3856	1600	p<0.05

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RHEUMATOLOGICAL IMMUNE-RELATED ADVERSE EVENTS ASSOCIATED WITH IMMUNOTHERAPY IN SOLID ORGAN TUMOR. STUDY OF 102 CASES FROM A REFERRAL SINGLE CENTER FOR LAST 4 YEARS

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Background: Immune checkpoint blockade therapy (ICBT) currently is one of the most used therapies against cancer. The activation of the immune system can lead to different immune-related adverse events (irAEs), being the rheumatological side effects among the most common.

Objectives: Our aim was to assess the rheumatological irAEs in patients who received immunotherapy.

Methods: We set up an observational study of patients treated with Nivolumab and Pembrolizumab (anti-PD1), Atezolizumab (anti-PD-L1) and Ipilimumab (antiCTLA-4) for solid organ tumors. All these patients were followed in a single reference University Hospital from March-2015 up to December-2018. The main outcome was to determinate the incidence of rheumatological irAEs.

Results: We studied 102 patients (63♂/39♀) with a mean age of 60.6 ±9.7 with different solid organ tumors. Only 7 patients (6.8%) had a previous diagnosis of an immune-mediated disease: psoriasis (n=2), psoriatic arthritis (1), systemic lupus erythematosus (1), spondyloarthritis (1), rheumatoid arthritis (1) and skin lupus (1).