

Disclosure of Interests: None declared


SEMAPHORIN 3A: A POSSIBLE MARKER FOR DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Sema 3A is concerned in the pathogenesis of many autoimmune diseases because it is involved in regulation of immune responses and maintenance of self-tolerance. Regulatory T cells play an important role in maintaining immunological self-tolerance by suppressing autoreactive T cells. Sema3A promotes regulatory T cells by enhancing IL-10 production.

Objectives: The current study aimed at testing the possible role of Semaphorin 3A (Sema 3A) in activity and in remission in rheumatoid arthritis patients and to assess whether this level correlates with interleukin 10 (IL-10) level.

Methods: Sixty Egyptian patients with rheumatoid arthritis (RA) were divided into three groups according to modified Disease Activity Score (DAS28), RA in high activity (group II, n=20), RA in moderate activity (group III, n=20) and RA in remission (group IV, n=20) and compared with 20 normal individuals (group I). Serum levels of Sema 3A and IL-10 were measured and correlated with ESR, CRP, Rheumatoid factor, DAS28 and Health Assessment Questionnaire (HAQ).

Results: Serum Sema 3A levels were significantly lower in high activity (55.7 ± 15.5 pg/ml) than in moderate activity groups (72.9 ± 14.6 pg/ml, p = 0.002) and both levels are lower than those in remission group (77.2 ± 13.1 pg/ml, p < 0.001 compared to high activity one) and the control groups (76.5 ± 23.6 pg/ml, p < 0.001 compared to high activity one also). A significant negative correlation was detected between Sema 3A and each of ESR, CRP, DAS28 and HAQ. Serum IL-10 was higher in RA patient groups, with highest mean among group IV.

Conclusion: reduced serum level of Sema 3A was found to be correlated with disease activity and indicating its usefulness marker for RA disease activity.

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GENE POLYMORPHISM TNFAIP3 RS6920220 IS ASSOCIATED WITH A SPECIFIC CYTOKINE PATTERN IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS

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Background: Genetic factors are known to substantially influence the production of cytokines. Objectives: This prospective study was aimed to explore whether the polymorphisms of immune response genes were associated with cytokines/chemokine production in patients with early rheumatoid arthritis (ERA) and whether a biological therapy affected this association.

Methods: 44 ERA patients (36 females; median age 55.0 [46; 60.0]; median disease duration 7.0 [4.0; 11.0] months; DAS28 5.9 [4.8; 6.4]) were included. 89% were positive for IgM rheumatoid, 92% - anti-CCP positive. All patients were treated with methotrexate and/or biological therapy in accordance with the treat-to-target strategy for 12 and 24 weeks after initiation of therapy. All patients were treated with methotrexate and/or biological therapy in accordance with the treat-to-target strategy (REMARCA study).

Results: Among all studied SNPs only polymorphism rs6920220 of gene TNFAIP3 was associated with a certain cytokine/chemokine production across all time-points: baseline, 12 and 24 weeks. At baseline, the carriers of GG genotype (27 pts) showed significantly higher serum levels of the following mediators, compared to the patients with GA/AA genotypes (17 pts): IL6 (42.8±23.0 pg/ml vs 25.5±8.4 pg/ml, p=0.001), TNFA (19.1±45.0 pg/ml vs 9.8±2.7 pg/ml, p=0.036), MIP-1α (19.1±45.0 pg/ml vs 117.6±47.2 pg/ml, p=0.013), MIP-1β (25.5±8.4 pg/ml vs 460.6 ±1826.0 pg/ml, p=0.018). At week 12, IL-6 serum levels were the only ones to remain associated with polymorphism rs6920220 (p=0.015).

Conclusion: The release of polymorphism rs6920220 of gene TNFAIP3 is linked to a particular cytokine/chemokine pattern. Biological therapy used according to the treat-to-target strategy for 24 weeks does not lead to the reduced production of IL-6, IP-10, MIP-1β, and PDGF-BB in the carriers of GG genotype.

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ACTIVIN A AND FOLLISTATIN AFFECT THE INTERACTION OF ENDOTHELIAL CELLS AND RHEUMATOID ARTHRITIS SYNOVIAL FIBROBLASTS

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Background: Activin A and its antagonist follistatin are part of a autoregulatory cycle, which is well known in the hypothalamic-pituitary-gonadal axis. Activins play an important role in autoimmune diseases, such as rheumatoid arthritis (RA). Due to inflammation, activin A is released systemically, causing an induction of its antagonist follistatin. The negative feedback mechanism is well described for hepatocytes, but seems to be inactive in synovial fibroblasts from patients with rheumatoid arthritis (RASF). Neangiogenesis, which is mediated partially by local fibroblasts, is increased due to inflammation and tissue hyperplasia in RA synovium. Despite the fact that RASF contribute to cartilage destruction in RA and RASF are able to interact with endothelial cells, less is known about the effect of activin and follistatin in this context.

Objectives: The aim of this study was to examine the effect of activin A and follistatin on the interaction of RASF and endothelial cells.

Methods: Endothelial cells (HUVEC) were commercially obtained and RASF were isolated from synovial tissue of patients with RA undergoing joint replacement surgery. RASF and HUVEC were stimulated in mono- or coculture with activin A (15ng/ml) or/follistatin (500ng/ml) and/or IL-1β (1ng/ml). The concentrations of activin A, follistatin, VEGF and IL-6 were measured by ELISA.

Results: IL-1β induced the release of activin A 8-fold in RASF alone (p < 0.01, n=5) as well as in direct coculture with HUVECs 4-fold (p < 0.05, n=5). The stimulation with follistatin together with IL-1β reduced the activin A concentration produced by HUVECs 9-fold (p < 0.01, n=5) as well as in cocultures (10-fold, p<0.01) in comparison to stimulation with IL-1β alone. This reduction could not be observed in RASF monocyte.

In HUVECs, the IL-6 release was reduced by 37.6% after stimulation with activin A and IL-1β (n=5,p<0.05) in comparison to the stimulation with IL-1β alone. In RASF monocyte the release of IL-6 was induced by 61.0% after stimulating with activin A combined with IL-1β in comparison to the stimulation with IL-1β alone. In direct coculture neither the induction, nor the reduction of the IL-6 concentration could be detected when stimulated with activin A and IL-1β.

The release of VEGF was induced in RASF with IL-1β (89%), activin A (55%), activin A combined with IL-1β (148%), follistatin and IL-1β (84%) compared to unstimulated control. In coculture with HUVECs, the induction was less distinct than in monocyte (IL-1β: 75%, activin A: 22%, activin A and IL-1β: 101%, follistatin and IL-1β: 67%, n=4).

Conclusion: The autoregulatory cycle of activin A and follistatin is active in endothelial cells and inactive in RASF. Due to the interaction of endothelial cells and RASF, the proinflammatory response of the RASF is weakened. This was shown in direct coculture with no induction in coculture compared to stimulation with activin A and IL-1β in RASF monocyte. Interestingly, in direct coculture, the effects of HUVECs appear to dominate resulting in a significant reduction of the activin A concentration in the presence of follistatin and IL-1β in comparison to RASF monocyte.

REFERENCES
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**AB0054**

**SEQUENTIAL INTRA-ARTICULAR INJECTIONS OF LINEAR AND CROSS-LINKED HYALURONIC ACIDS IN THE TREATMENT OF GONARTHROSIS**

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**Background:** Sequential intra-articular injections of linear and cross-linked hyaluronic acids in the treatment of gonarthrosis

**Objectives:** This study evaluates clinical and biochemical effects of sequential intra-articular (IA) injections of two different formulations of hyaluronic acid (HA) in gonarthrosis (GA) patients. The first formulation consists in linear HA (LHA, MW 800-1200kDa; Regenflex Starter, Regenyal Labs, Italy) and the second in an intercalated mixture of cross-linked and linear HAs (CL-LHA, MW 1-2 MDa the crosslinked form and 500kDa the linear, intercalated one; Regenflex BioPlus).

**Methods:** 39 knee GA patients, 19 adults (50–65 years) and 20 elderly (65 years) underwent two IA injections, i.e. LHA only at baseline and CL-LHA after 1 week. The same injections were repeated after 6 months. Clinical assessment - visual analogic scale (VAS) for pain, range of motion (ROM) and WOMAC index for knee functional limitation - was performed at baseline and after 3, 6, 9, 12 months. Blood, collected at baseline, after 1 week and 3 months, was analysed for relevant cytokines and collagen telopeptide II (CTX-II). Synovial fluid (SF) from patients with recurrent knee effusion (GA worse group) was biochemically analysed at baseline and 1 week. SF proteomic analysis was also carried out at specific time points.

**Results:** This HA-regimen improved joint pain and function independently from the age; plasma and synovial biochemical analyses indicate the attenuation of inflammatory cytokines (IL-1β, IL-9 and IL-17) and the stabilization of CTX-II; ultrasonograph data show an improvement of cartilage conditions and thickness at 12 months.

**Conclusion:** Sequential IA injections of LHA and CL-LHA represent a highly effective treatment especially in low degree GA patients and produce a significant and perduring improvement also in the GA worse group. The efficacy is likely dependent on the sequential administration of LHA and CL-LHA: the pharmacokinetic rationale of this combination will be discussed.

**References:**
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**AB0056**

**CUTANEOUS ADVERSE EFFECTS WITH BIOLOGIC AGENTS**

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**Background:** Biologic agents (BA) are designed to treat chronic inflammatory diseases (CID), however, the adverse effects inherent with these drugs are more and more encountered. Among them are dermatological manifestations: infections, allergic reactions or even skin cancers, which sometimes require stopping treatment temporarily or permanently.

**Objectives:** The goal of this work consists to identify the cutaneous manifestations (CA) that have been reported to the most commonly used biologics in CID. Methods: It's a prospective study in patients received in day hospital and treated with BA for CID during a period of 9 months (October 2017 - June 2018), we recorded all the data on CA after a complete dermatological examination, not forgetting that we appreciated the prototype of the patients, the level of exposure to the sun and means of photoprotection.

**Results:** We collected the data of 68 patients under BA for the study (Adalimumab = 21, Etanercept= 17, Tocilizumab = 2, Infliximab = 7, Rituximab = 11) with a clear female predominance 59.4%, the mean age was 39 years. 37 (54%) had cutaneous manifestations, the main CA occurred with TNFα inhibitors 21/68 (30%), with more often skin infections. The other CA encountered were cutaneous rashes and allergic reactions, appearance of psoriasis or eczema and injection site reactions, we didn't cross any skin cancer.

**Conclusion:** Cutaneous manifestations remain frequent and relatively benign with BA. This work confirms the importance of education and dermatological monitoring of patients treated with biologic drugs in the CID. This prospective study needs to be completed over a longer period especially to screen any skin cancer.

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**AB0057**

**ASSESMENT OF MATRIX METALLOPROTEASE 3 (MMP3) AS A POTENTIAL BIOMARKER FOR RHEUMATOID ARTHRITIS IN ALGERIAN PATIENTS**

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**Background:** Matrix metalloproteinase 3 (MMP3) is a protease induced by rheumatoid pannus pro-inflammatory cytokines during rheumatoid arthritis (RA) and degrades many cartilage and bone components. Its serum level is a useful marker for predicting joint destruction and evaluating disease activity.

**Objectives:** First, compare MMP3 production in RA patients to controls, then try to place this marker in the evaluation of disease activity.

**Methods:** We subdivided the studied patients into three groups:
- **RA:** n = 134; sex ratio: 1: 5; age: 50 ± 14 years; disease duration: 7 ± 9 years,
- **Healthy controls:** n = 67; sex ratio: 1: 7; age: 38 ± 11 years,
- **Population control:** Patients with:
  - **Inflammatory rheumatism:** n = 80,
  - **Chronic inflammatory diseases (CID):** 18 Connective tissue disease (CTD), 14 chronic hepatitis C and 2 Crohn disease (CD).