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THE EFFECT OF ANTI-IGE THERAPY IN KNEE OSTEOARTHRITIS: A PILOT OBSERVATIONAL STUDY

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Osteoarthritis is a whole-joint disease and its pathogenesis remains poorly understood. Recent evidence proposed the importance of the innate immune system as trigger of synovium inflammation following the degeneration of cartilage. Moreover, synovial mast cells (MCs) might be correlated with pain and disability reported by patients. Anti IgE therapy represents a new class of MCs stabilizing agent, licensed for people with asthma and chronic urticaria. Therefore, we studied if the stabilizing effect of anti IgE would improve the pain and disability in patients affected by knee osteoarthritis and atopic disease. This pilot study provides the first evidence that anti IgE treatment induces a short-term clinical improvement supporting the role of MCs in osteoarthritis.

Osteoarthritis (OA) is the most widespread form of arthritis, typically seen in elderly patients affecting all joints (1). Originally seen as a cartilage only disease, OA should be considered an inflammatory illness involving cartilage, bone and synovium (2).

It has been established that synovial inflammation plays a key role in symptoms and pathophysiology of OA (3). An interesting field of research questioned the triggering of synovium activation and the pathways that characterize the inflammatory response. Recent data suggest that the damage of cellular and cartilage extracellular matrix, produced from trauma, instability, deformity, microtrauma, meniscopathies or normal aging in OA, generates damage-associated molecular patterns (DAMPs) that might activate the

innate immune system by Toll-like receptors (TLRs) (4).

TLR activation is an important stimulus for NFkB activation and subsequent production of chemokines and cytokines, which recruit macrophages, granulocytes and lymphocytes in synovium (5). TLRs are constitutively expressed by a variety of innate immune cells including macrophages and mast cells (MCs). It has been established that pain in OA is correlated to the inflammation grade of synovium (6) and several researches pointed out the relationship between clinical symptoms of OA and the abundance of MCs in inflammatory infiltrate of synovial specimens. For these reasons, several researches began to investigate the possible role of

Key words: osteoarthritis, synovial mast cells, Omalizumab

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0393-974X (2016)

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MCs in OA, in order to assess future therapeutic challenges (7).

MCs can be considered “sentinels” of the innate immune system, ready to take action in response to antigens, infection and other stimuli (8). These stimuli are either Ig-E and non Ig-E mediated (9). Anti IgE therapy represents a new class of MCs stabilizing agents that attenuates the degree of responsiveness of MCs to stimulators. Omalizumab (Xolair[®], Novartis, Camberley, United Kingdom) is a recombinant humanised IgG1 monoclonal antibody that targets circulating IgE. It represents a safe biological therapy for treating patients with asthma or chronic urticaria who are not being adequately treated with standard therapy (10, 11).

The aim of this study was to assess any changes of knee pain and disability in patients affected by knee OA in therapy with Omalizumab in order to look for more evidence supporting the role of MCs in OA.

MATERIAL AND METHODS

This prospective, single-center, pilot study was conducted with the highest respect for individual participants. All patients included in our study, in treatment with Omalizumab, were prospectively evaluated at 0, 3 and 6 months from the beginning of anti IgE therapy.

Inclusion criteria were: Asthma allergic or chronic urticarial not responsive to standard therapy and symptomatic knee osteoarthritis with radiographic imaging findings of degenerative joint changes (Kellgren-Lawrence grade I-IV). Exclusion criteria were: use of intraarticular corticosteroids or viscosupplementation from 3 months before the start of anti-IgE therapy to the entire follow-up period, use of NSAIDs or nutraceutical supplements in the 3 weeks before treatment and during follow-up period, rheumatic diseases, osteonecrosis.

All patients were treated in the Azienda Ospedaliera-Universitaria Ospedali Riuniti of Ancona (Italy), in particular, regarding OA, each patient was referred to the Clinic Orthopedics, meanwhile regarding atopic disease,

they were referred to the Allergy unit. During each visit, each patient was assessed by measurement of the subjective knee pain, rated on a visual-analogue scale of 100 mm (EQ VAS) and by measurement of joint disability scored by KOOS (Knee injury and Osteoarthritis Outcome Score) latest version available 2012.

All patients received a series of instructions after every injection. In case of knee pain during the treatment and follow-up period, patients were recommended to not use any analgesic medications but only cold therapy and limiting the use of the knee for at least 24 h. Obviously, if patients could not handle the pain, the use of any medication to relieve it made them unsuitable for the study. Mild activities were indicated and sport or recreational activities was allowed as tolerated. The Student *t*-test was performed for the KOOS score and the EQ VAS to compare pre- and postoperative values. Data are expressed as means with standard deviations (SD). For all tests, $p < 0.05$ was considered significant for a one-tailed tests.

RESULT

From September 2016 to February 2017, 42 patients followed by Allergy unit of Ospedali Riuniti, Ancona, under anti-IgE treatment, were assessed for eligibility. The study sample consisted of 10 patients, 9 women and 1 man, mean age 60.2 ± 11.77 . Seven patients were affected by allergic asthma, while 3 patients had chronic urticaria. All of them had symptomatic knee OA. Each patient included in the current study received six subcutaneous injections of Xolair[®] at a 4-week intervals and no further injection during the follow-up period. Regarding patients affected by allergic asthma, 3 patients received 600 mg of Xolair in each injection, two patients 300 mg, one 150 mg and one 450 mg.

On the other hand, patients with chronic urticaria, received 300 mg of Xolair in each injection. All patients completed the follow-up at 6 months. The radiological classification, according to the Kellgren and Lawrence criteria (KL) by two experimenters,

allowed to stratify the sample of the study: 2 patients (20% of the sample) had I degree, 5 patients (50% of the sample) II degrees and 3 patients (30%) III degrees.

In regards to the overall clinical effect of the Omalizumab in knee OA, there were statistically significant differences in pre- and post-treatment values of EQ VAS and KOOS ($p < 0.05$) (Fig. 1). The values of mean $\pm$ SD of EQ VAS at baseline were 64.34 ± 9.64 , at 3 months follow-up 40.94 ± 6.38 , at 6 months follow-up 37.5 ± 7.07 . The values of mean $\pm$ SD of KOOS at baseline were 43.3 ± 5.3 , at 3 months follow-up were 73.4 ± 6.2 at 6 months follow-up were 75.8 ± 5.8 .

DISCUSSION

Omalizumab has multiple pharmacologic and immunoregulatory effects (12). It has been reported that the administration of anti IgE reduces IgE

concentrations in the blood and tissue. Moreover, anti IgE treatment gradually decreases the density of IgE-Fc ϵ RI on MCs by 95% within a few months (13). Considering the ability of anti IgE treatment to reduce the release of mediators following MCs activation and the promising role of MCs in OA, we wondered if the stabilizing effect of Omalizumab on MCs would change the pain and disability in knee osteoarthritis. Our data showed that patients in therapy with Omalizumab, affected by knee OA, had a statistically significant improvement in reducing pain and recovering articular function from basal evaluation to 3- and 6-month follow-up visits.

To date, a growing evidence suggests the potential role of MCs in inflammatory arthritis (14), but at the same time, recent investigations questioned if MCs might be implicated in OA clinic and pathogenesis (7). Following their activation, a wide range of mediators, both preformed and newly produced, are

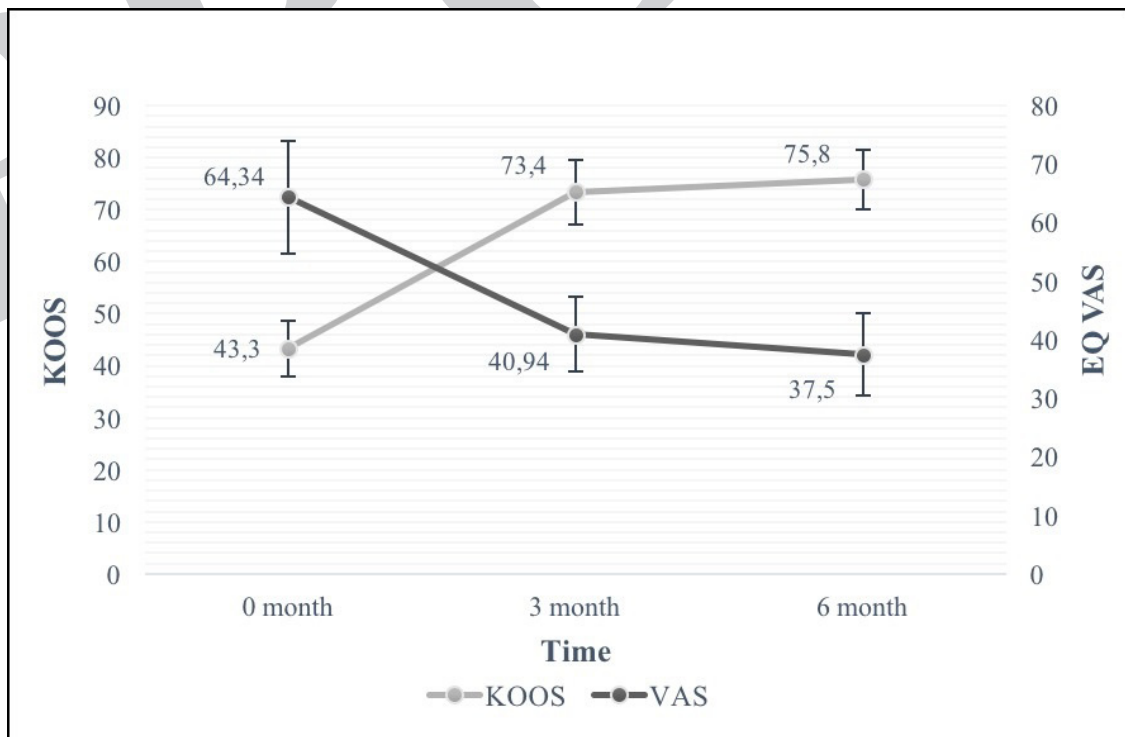


Fig. 1. Pre- and post-treatment values of EQ VAS and KOOS.

released. Some of these mediators, such as histamine, cytokines and neurotrophins (e.g. NGF) might contribute to the synovium inflammation and pain reported by patient. Although the most conceivable and latest theories of OA pathogenesis implicate that the activation of the innate immune system as MCs is mediated by TLRs (15), we can hypothesize that in these atopic patients, the improvement of clinical data were due to the partial blockage of MCs activation, via IgE related. This is not surprising, considering that the mechanisms involved in MCs activation or recruitment in OA could be very different. However, these results have limitations. First, only a small cohort of patients was included, because the majority of patients in treatment with Omalizumab were too young to be affected by OA.

It would be interesting to understand if Xolair might be effective to decrease the prevalence of OA in atopic patients, supporting the role of MCs in the pathogenesis of the disease. Moreover, these data were obtained in a hypothesis generating setting and require replication. Secondly, we did not analyze the serum of these patients and we did not know if the improvement was correlated to the amount of IgE in serum.

To the best of our knowledge, no research has been conducted to underline the differences of OA in atopic and non-atopic patients, regarding synovium inflammation and characterization of inflammatory infiltrate. Therefore, the role of MCs in the different subtypes of OA is still unclear. Even considering these limitations, the results of our study are quite intriguing.

We presented evidence suggesting that the activation of MCs might be correlated to the pain and disability reported by patients. Hence, it could be hypothesized that future biological therapies involving IgE activation pathways might be useful tools to lead symptomatic improvement through inhibition of MCs degranulation and reduction of synovium inflammation (16).

Thus, additional research is required to understand the interplay between MCs, synovitis and activation of innate immune system in OA.

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