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Case Report Open Access

Abatacept therapy for Rheumatoid Arthritis in patients with Hepatitis C Virus infection comorbidity: A Series of Four Patients

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Abstract

Patients with rheumatoid arthritis (RA) and hepatitis C present a diagnostic dilemma due to the viral induced immunogenistic response with subsequent biomarkers and an associated arthropathy that is difficult to distinguish from RA. They also present as a treatment dilemma due to restrictions in the use of disease modifying anti-rheumatic drugs that are standards of care such as methotrexate and leflunomide. Unfortunately they are often excluded from clinical trials in our newer RA therapeutics. In terms of biologics, beyond the American College of Rheumatology recommendations for tumor necrosis factor inhibitors, there are only case reports in alternate classes of biologic therapies. In this case report, four patients with hepatitis C are followed in terms of safety and efficacy while on abatacept (a soluble fusion protein that works as selective costimulation modulator inhibiting the activation of T cells) to treat their rheumatoid arthritis. Although each patient had varying benefit to the abatacept therapy, no patient had adverse reaction to infusion, or intolerance, and it did suggest the potential use of abatacept in this patient population.

Keywords: Abatacept therapy; Rheumatoid arthritis; Hepatitis C; Virus infection

Introduction

Rheumatoid arthritis (RA) is a disease that is potentially debilitating, disabling, and disfiguring. It effects nearly 0.5%-1% of the population worldwide [1] and is with estimates of nearly 1.3 million affected in the United States [2]. Treatment of the disease has been advanced dramatically over the years with newer therapeutics. However there are specific patient subsets that are not as well studied in regards to many of our newer biologic agents, specifically in regards to patients with Hepatitis C.

Infection with the hepatitis C virus (HCV) represents a growing problem throughout the world with an estimated 170 million people infected worldwide and 3 million in the United States. Out of these, approximately 40,000 also have rheumatoid arthritis [3].

HCV is associated with a number of extrahepatic manifestations, of which rheumatologic complaints are the most common. In a large, prospective study of 1,614 HCV-infected patients, arthralgias were the most common complaint, with a reported prevalence of 23% [3]. A symmetric, inflammatory polyarthritis primarily involving small joints, which resembles rheumatoid arthritis (RA), has been described. Rheumatoid factor may be present in up to 50-85% of these patients; however, unlike RA, no erosive joint changes are noted [3].

These patients, and the providers that care for them, must contend with more than one potentially life-shortening illness, difficulties with diagnosis and the realization that not all treatments available to them have proven performance and safety in their disease combination. There are several ways that hepatitis C can alter a rheumatologist's ability to diagnose RA. Many patients with hepatitis C may have positivity for rheumatoid factor. HCV treatments can cause joint pain and swelling, looking very much like rheumatoid arthritis. Hepatitis C causes patients to have lower levels of anti-CCP antibodies [4]. Therefore, clinico-serological and virological work-up is highly mandatory in patients presenting with chronic arthritis [5].

Not only do these patients present a diagnostic dilemma due to the viral induced immunogenistic response with subsequent biomarkers and an associated arthropathy that is difficult to distinguish from RA, but they are often excluded from clinical trials in our newer RA therapeutics.

Usually, HCV-associated rheumatoid arthritis is poorly aggressive and may respond to low doses of steroids and hydroxychloroquine (HCQ). Patients may then be treated with the standard disease modifying therapeutic strategies for RA, with precautions for the liver, in particular excluding methotrexate and leflunomide. The American College of Rheumatology has recommended that the tumor necrosis factor inhibiting drugs (etanercept, infliximab, adalimumab, golimumab and certolizumab) can be used in patients with chronic hepatitis C without causing worsening of liver function [5]. One study also suggests that rituximab, and cyclosporine A seem to have a potential synergistic effect in association with antiviral treatment (IFNα+RIBA) [6]. But what if antiviral treatment is complete, viremia low but RA remains problematic? This leaves many rheumatologists concerned about what other treatment options are available.

In this case series we will be following safety and efficacy in four patients given abatacept.

Abatacept is a soluble fusion protein that consists of an extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to a modified Fc portion of human IgG1. It acts as a selective costimulation modulator, by binding to CD80 and CD86, blocking the interaction with CD28 and thereby inhibiting the activation of T cells. In vitro this has shown to decrease the cytokines TNFalpha, IFN-gamma, and IL-2, and in clinical trials decreasing

serum levels of soluble IL-2 receptor, IL-6, RF, CRP, matrix metalloproteinase-3 and TNFalpha [7].

In patients with hepatitis C, T-cell response plays a role in viral clearance as well as viral persistence. At this point there is little data following patients with RA treated with abatacept and concomitant HCV. Only one other case report was noted on PubMed search with two cases. This is only the second case report published at this time, unique in that two of the four patients were previously treated with anti-viral therapy one with resolution of viral load.

Cases

Patient A

Patient A presented to our rheumatology clinic June 5th, 2007 as a 60 year old male with complaints of fatigue and morning stiffness lasting 1-2 hours. He complained of joint pains beginning approximately 2 years prior, peripheral neuropathy with negative EMG/NCS unresponsive to pregabalin, and hepatitis C diagnosed years ago. At the time of his hepatitis C diagnosis viral load had been over a million. He underwent treatment with PEG-IFN with his most recent viral load at presentation of 183,000. His rheumatoid factor was elevated at 42, CCP negative, ANA+1:40, +SSA, +EBV early antigen and negative cryoglobulins and hepatitis B screening. An MRI of the right hand and wrist showed synovial effusion of the wrist, and erosions at the MCP heads. He was diagnosed with rheumatoid arthritis and initially started on hydroxychloroquine and prednisone and responded well with tapering doses of prednisone. In September 2007 he underwent a 6 month regimen for chronic EBV with famciclovir. In October 2007, the patient had increased joint pains with weaning off the prednisone. He did not wish to continue the hydroxychloroquine, and he was started on adalimumab. In February of 2008 he developed injection site reactions to adalimumab with worsening in his morning stiffness and it was decided to switch therapy to abatacept. April 2008 he did well with the loading doses with improvement in his pain, stiffness and fatigue and he was again able to start tapering his doses of prednisone. By June 2008 he was down to every other day dosing of 2.5mg prednisone and his abatacept dose was increased to 1000 mg. Around this time he was hospitalized for acute coronary syndrome and cardiac stenting. By July 3rd 2008 he continued to do well off all doses of prednisone with abatacept monotherapy. By the end of that month however he began to have increased pain, synovitis, fatigue, and stiffness. His hydroxychloroquine was restarted. In September 2008 he had increased fatigue and stiffness; he was again restarted on 6 months of valacyclovir for continued elevation in early antigen EBV. In November 2008, the patient had increased synovitis and pain, it was felt abatacept was no longer effective and the patient was switched to another biologic agent.

Patient B

Patient B presented in February 2006 for re-evaluation of polyarthralgias as a 51 year old female. She had been seen previously in 2002 for a diagnosis of fibromyalgia and possible lupus with a positive ANA and dsDNA, however had been lost to follow up. Upon her re-evaluation she had complaints of two to three months of worsening pain in her neck, hands, wrists, forearms, and hips with morning stiffness lasting longer than an hour. She also had complaints of possible photosensitive rash and exam findings of synovitis in wrists, ankles, shoulders. Updated labs had shown a negative RF, CCP, ANA, dsDNA, as well as hepatitis B screening however she had a positive hepatitis C screen. X-rays had shown degenerative and nodal osteoarthritis but no overt erosive disease. The patient was unable to have MRI performed due to financial constraints. She was started on hydroxychloroquine and referred to GI to discuss HCV treatment options. Over the course of the next few years the patient continued with significant joint pain, swelling and stiffness as well as chronic widespread musculoskeletal pain. She had been off and on daily prednisone or short courses and in 2007 she was trialed on adalimumab to treat rheumatoid arthritis like disease. She remained on the adalimumab for 6 months and was later discontinued after increased infections and poor efficacy. The patient deferred further biologics for fear of infectious processes and had been maintained again on daily steroid to help with joint swelling and stiffness; she later did agree to give a trial of minocycline in July 2008. Although she did feel this provided her some benefit, she reconsidered a biologic agent in April 2009 and was started on abatacept. She had a significant improvement in her joint swelling and stiffness with the abatacept infusions and remained on this until July 2010 at which time it was stopped for a mastitis infection. At the last couple of infusions the patient had felt she had gotten less articular benefit than previous and when she was cleared from infectious process she elected to discontinue this biologic agent. Although the patient had been following with GI and HCV treatment options were discussed with her, either she or they never elected to consider the start of treatment. Chronic widespread pain had been a difficult issue for the patient throughout her treatment, exacerbated by stress from her work, anxiety, depression, and self-escalation at times of her narcotic pain medications. An MRI was able to be performed later in 2011 of her right wrist with synovitis and erosions consistent with an erosive inflammatory arthropathy.

Patient C

Patient C initially presented to our rheumatology clinic as a 54 year old female in March 2009 with polyarticular complaints of pain, and prolonged morning stiffness. She had a history of +ANA in the past and was given a trial of hydroxychloroquine back in 2007 with another provider but it was stopped after several months without benefit. The patient was also concerned it may have been causing ocular symptoms; she did not remember a previous diagnosis. Updated testing showed a +ANA>1:1280, +RF at 19, negative dsDNA, CCP, antiphospholipid antibodies and SPEP. Her hepatitis C screen was positive with AST and ALT (Figures 1 and 2) over three times the upper limit, Hepatitis B screen was negative. X-rays of the hands showed joint space narrowing and subluxation of the left third MCP joint. An MRI of the left wrist showed multiple large erosions involving the carpals, distal radius and MCP heads in view. There was joint effusion of the wrist and tenosynovitis appreciated as well. The patient was diagnosed with rheumatoid arthritis and started on infliximab which was initially effective for her pain and stiffness. During her time on the infliximab she had to increase her dose and frequency to q 4 weeks and was on 7mg/kg dose. She would periodically have need for courses of prednisone to help treat flares. She had her infliximab held at one point for a cervical fusion and later for a MRSA infection of her lacrimal gland. By October 2010 she developed severe pain, and swelling of her left wrist, an MRI was obtained with abnormal signal throughout the wrist worrisome for a significant inflammatory process such as severe reactive inflammatory arthritis or infectious process, erosions were present as was synovial thickening with complex fluid identified in the mid carpal and radioulnar space. Joint aspiration was

negative for infectious process; the patient was treated with IV methylprednisolone with quick resolution of her symptoms. She was then switched to abatacept from infliximab in November. By December she developed right hand and wrist swelling and pain similar to the left side previously. An MRI was obtained with extensive edema throughout the carpals and 2nd-5th metacarpals suggesting reactive edema from flare/ severe inflammatory arthritis versus infectious arthritis, joint effusions and erosions were also noted. The patient had been referred to GI for significant elevation in liver function tests in August and October and did not see them until December. They felt her LFTs were elevated secondary to medications, fatty liver as well as her hepatitis which was found to be genotype 1A. The patient had historically deferred treatment due to her depression and did not want to start treatment at this time. The patient was only continued on the abatacept for four infusions and requested to go back to her previous biologic as she felt it provided her more benefit.

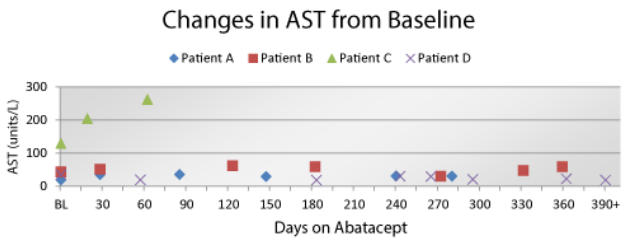

Figure 1: Changes in AST from Baseline.

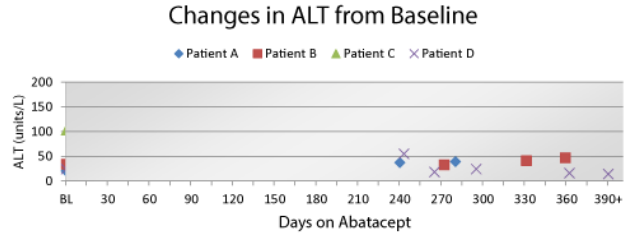

Figure 2: Changes in ALT from Baseline.

Patient D

Patient D initially presented July 2007 to rheumatology clinic as a 44 year old female for evaluation of a +RF at 254. She had complaints of morning stiffness lasting half the day, pain in her hands, wrists and feet, swelling and significant fatigue. During work up earlier that year she was also found to have hepatitis C which was concurrently under treatment with Pegasus INF and ribavirin and told she was responding well. Other treatments for her pain at that time had included oxycodone, hydrocodone, celecoxib and a muscle relaxer. Lab work up showed continued elevation in RF at 158, negative CCP, negative ANA and sjogrens antibodies, as well as negative cryoglobulins and hepatitis B screening. X-rays of the hands revealed peri-articular osteopenia, MRI of the right hand and wrist showed erosions in carpals and proximal phalanx of the 4th digit. She was diagnosed with rheumatoid arthritis and initially started on prednisone and hydroxychloroquine with a taper of the prednisone. By October 2007 she discontinued treatment of her HCV due to intolerance; viral load was undetectable however her gastroenterologist recommended 5 more months of treatment. Pain, swelling and stiffness became an issue for her however, and she had developed leucopenia from the anti-viral treatment. As soon as this resolved she was started on adalimumab in December 2007. Adalimumab had efficacy off and on, however after starting prednisone and later sulfasalazine even increasing dosing frequency, the patient ultimately failed this biologic and she was started on abatacept infusions. She got her first infusion in June 2008, however her next infusion was placed on hold as a renal biopsy in the interim was concerning for a malignant process and she was bridged therapy with prednisone until she discontinued this secondary to weight gain. By December the patient underwent a partial nephrectomy and it was actually found to be a benign adenoma therefore she was resumed on the abatacept. This did help improve her symptoms. Unfortunately throughout the patient's treatment for her RA, she had significant pain and debility from spinal stenosis, and fibromyalgia exacerbated by difficult to control anxiety and depression. The abatacept was again held in September for another potential renal process however in December oncology felt it was a benign cyst and she again resumed her abatacept. When she resumed the abatacept in January 2008, she noted slower improvement in her RA symptoms than before. Throughout January to July 2010 she continued to do well with her RA on the abatacept however continued with chronic pain and worsening psychiatric issues. In July she developed widespread rash/ excoriations on her arms, which was exacerbated by picking as well as some worsening in her symptoms. In September she was started on minocycline. In November 2010 it was felt the abatacept was no longer providing her significant benefit and it was decided to switch her biologic agent. At that time her viral load continued to be undetectable.

Discussion

This case report of 4 patients with both hepatitis C and rheumatoid arthritis follows their disease and treatment with abatacept therapy. Each patient had varying benefit to the abatacept therapy although no patient had adverse reaction to infusion, or intolerance. There did not seem to be an adverse effect to liver enzymes or viral loads for the patients in which viral loads were followed. In all four cases the patients had failed oral DMARD, as well as one TNF inhibitor and had requirements for glucocorticoids.

This disease population can be quite difficult as a hepatitis C associated arthropathy may not only mimic rheumatoid arthritis but may also exist concomitant with rheumatoid arthritis. Although a CCP antibody may be useful for differentiation, as in case A, C and D these patients did not make a CCP antibody, and their diagnosis was aided by MRI findings of an erosive arthritis consistent with rheumatoid arthritis. Case B also had an MRI performed at a later date which was also consistent with an erosive arthritis such as rheumatoid arthritis, although treatment had been begun based on clinical diagnosis earlier on in her disease course.

Since hepatitis C is a relatively common chronic viral infection affecting the diagnosis and treatment of rheumatoid arthritis, rheumatologists must work closely with liver specialists to monitor patients while being as aggressive as possible in treating the potentially disabling disease, rheumatoid arthritis. While the tumor necrosis factor inhibiting agents appear to be safe and effective in those with RA and hepatitis C, with rituximab and cyclosporine helpful during anti-viral treatments, [8] non-responders and the rheumatologist's

that care for them, need other biologic treatment options (Figures 3 and 4).

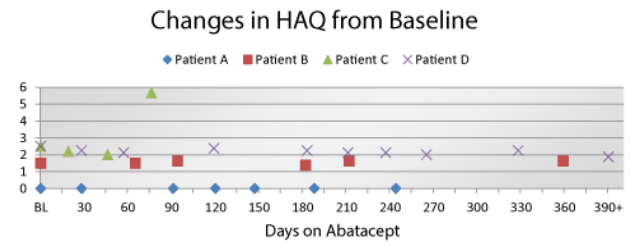

Figure 3: Changes in HAQ from Baseline.

Although the results of this case report suggest the potential use of abatacept in a patient population with hepatitis C as tolerated and potentially efficacious, this would have to be confirmed with controlled and randomized trials and/or large observational studies for confirmation.

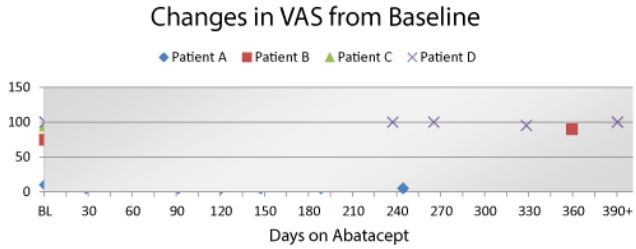

Figure 4: Changes in VAS from Baseline.

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