



Krishnadas, R., Krishnadas, R. and Cavanagh, J. (2010) *Sustained remission of rheumatoid arthritis with SSRI antidepressant: a case report and review of literature*. Journal of Medical Case Reports

<http://eprints.gla.ac.uk/40904>

Deposited on: 19 October 2010

Title: Sustained remission of rheumatoid arthritis with SSRI  
antidepressant: a case report and review of literature

Authors

**Rajeev Krishnadas**

Sackler Institute of Psychobiological Research

University of Glasgow

Southern General Hospital

Glasgow

G12 8RR

Rk60s@clinmed.gla.ac.uk

**Ranjit Krishnadas**

Amrita Institute of Medical Sciences and Research Centre

Amrita Lane

AIMS Ponekkara Post

Kochi, Kerala 682 041

India

Ranjit.krishnadas@gmail.com

**Jonathan Cavanagh**

Sackler Institute of Psychobiological Research

University of Glasgow

Southern General Hospital

Glasgow

G12 8RR

j.cavanagh@clinmed.gla.ac.uk

Corresponding author:

**Rajeev Krishnadas**

Sackler Institute of Psychobiological Research

University of Glasgow

Southern General Hospital

Glasgow

G12 8RR

Rk60s@clinmed.gla.ac.uk

## **Abstract**

### Introduction:

The mainstay of pharmacological therapy of Rheumatoid Arthritis includes the use of disease modifying agents (DMARDS) like sulphasalazine and methothrexate, and more recently anti TNF alpha agents. Depression remains a major co-morbidity in patients with Rheumatoid arthritis and is thought to contribute to disability and mortality in these patients. There is now evidence to suggest that a biological link exists between substrates responsible for inflammatory conditions and mood disorders. Most of this evidence comes from preclinical studies. Nevertheless, more research into this area is helping us understand the possible mechanisms through which these conditions interact with each other.

### Case presentation:

We describe a 60 year old Indian man with rheumatoid arthritis diagnosed 15 years ago who had minimal response to multiple therapies with DMARDs, whose arthritis symptoms surprisingly remitted when he was started on an specific serotonin reuptake inhibitor (SSRI) antidepressant, 3 years ago, for co-morbid major depression. This remission has been maintained on this medication and the patient is currently not on any antirheumatoid medications.

### Conclusion:

Possible mechanisms linking substrates of mood disorders and inflammation are reviewed in this case report, particularly the serotonergic system. There seems to be evidence for a significant interaction between the serotonergic systems and inflammation. This interaction seems to be bidirectional. An understanding of this relationship is most important to gain insight not only into pathophysiological mechanisms underlying these condition, but also into how treatments for these conditions may compliment each other and possibly provide greater therapeutic options in both these disabling conditions.

## Introduction

Rheumatoid arthritis (RA) is a chronic, disabling condition that primarily affects joints producing an inflammatory synovitis that often progresses to destruction of the articular cartilage and ankylosis of the joints. Prevalence of RA is 1.16% in women and 0.44% in men in the United Kingdom.[1] Similar prevalence has been reported in India. [2] The mainstay of pharmacological therapy of Rheumatoid Arthritis includes the use of disease modifying agents (DMARDS) like sulphasalazine and methothrexate, and more recently “biological agents” like anti TNF alpha agents. [3]

Conservative estimates suggest that major depressive disorder affects between 13% and 17% of patients with rheumatoid arthritis (RA). [4] Major depressive disorder is thought to be an independent risk factor for both work disability and mortality in those with RA.[5] Clinical associations between medical illnesses and major depressive disorder are not solely attributable to illness induced disability or pain. There is a growing body of evidence implicating mechanisms involved in a bi-directional link between biological substrates of mood disorders and inflammation. Low dose tricyclic antidepressants (TCA) have long been a part of the armamentarium to treat pain and sleep disturbance in this population. Few studies have reported the effectiveness of SSRIs in this condition.

Here we describe a patient with RA, whose disease remitted completely

with an SSRI started for an episode of Major Depressive disorder.

### **Case Presentation**

A 57 year old Indian man (90kg/170cm) with a history of Rheumatoid arthritis, presented with features suggestive of a severe depressive episode in 2007. He had no previous or family history of depression. He was first diagnosed with RA in 1993 and was treated with sulphasalazine and diclofenac for 6 years. He gradually developed resistance to these drugs with persistent synovitis, progressing joint deformities, elevated ESR and CRP. There was an acute exacerbation of the illness in 1999 during which he was switched on to a methotrexate regimen thrice weekly with partial response. He developed severe anaemia and related angina on methotrexate and had to discontinue the medication in the year 2002. Since the episode of angina, the patient was started on a daily regimen of low dose aspirin at 75mg and simvastatin at 40mg. He continued to take various NSAIDs without much effect up until 2007, when he presented to his clinician with an episode of severe depressive illness. He was referred to a psychiatrist, who started him on escitalopram, a serotonin specific reuptake inhibitor, at 10 mg a day and risperidone, an antipsychotic with a serotonin dopamine antagonist action at 1 mg a day. Risperidone was started as the patient showed significant ruminative thoughts almost bordering on delusions. During this period, he was also on the low dose aspirin and simvastatin.

Since the episode of depression was severe, it was decided to maintain him on the antidepressant medication for at least a year after complete remission of his depression. Prior to starting the patient on escitalopram and risperidone, his DAS 28 score was 6.6, suggesting that his arthritis was far from being under control. On this combination, along with an improvement in his depressive symptoms, the patient also perceived significant improvement in his arthritis symptoms within a period of 3 to 4 weeks. Risperidone was gradually tapered and stopped after 2 months. His pain, morning stiffness and fatigue continued to improve on escitalopram. Initially, the perception of improvement in arthritis symptoms was attributed to the improvement in his mood. However his end of the year rheumatology assessment showed that his DAS 28 scores had significantly improved to 2.2, being in the remission criteria range suggested for the Indian population. [6] After a period of one year on escitalopram, it was decided to gradually taper and stop his antidepressants. On stopping the antidepressants, his joint pain and stiffness started to worsen and in two weeks time, at the patient's request, he was recommenced on 10mg of escitalopram and has since been maintained on the same to date. His arthritis has been under remission since.

## **Discussion**

SSRIs have been found to be effective in treatment of depression in RA. [7] Recently Baune and Eyre reported a case of rheumatoid arthritis that responded to a combination of SSRIs and antipsychotics.[8] Our case



differs from Baune and Eyre's report in that the patient was taken off the risperidone (antipsychotic) in 2 months time, but continued to maintain his remission. Further, his arthritis symptoms relapsed when his escitalopram was stopped, and improved when it was restarted. What is more interesting is that the patient continues to be under remission in spite of not being on any disease modifying agent or anti-inflammatory medications (other than low dose aspirin at 75mg and simvastatin at 40mg). It should also be noted that the patient was on the combination of aspirin and simvastatin from 2002 to 2007 without any improvement in inflammatory symptoms.

There seems to be a bidirectional relationship between biological substrates of mood disorders and inflammation. For e.g. inflammatory mediators like proinflammatory cytokines are thought to have a direct impact on biological substrates thought to be involved in the pathophysiology of mood, particularly the serotonergic system and conversely, serotonergic pathways are thought to be important in mediating both inflammation and mood.

## I. Inflammation modulates serotonergic system

### a. Inflammation upregulates serotonin transporter:

A key site of action of antidepressants is the serotonin transporter (SERT), which regulates serotonergic neurotransmission. Data from preclinical studies indicate that both density and activity of SERT are increased by proinflammatory cytokines, (e.g.  $\text{TNF-}\alpha$ ), leading to an increase in 5HT

uptake from the synapse, thus decreasing 5HT transmission. [9] This regulation of neuronal SERT activity occurs via p38 mitogen activated protein kinase -linked pathways. Data from our group confirm this hypothesis. Treatment with TNF blockade agent Adalimumab led to a decrease in serotonin transporter binding by upto 20% using [123I] Beta CIT - SPECT. [10]

b. Inflammation activates kynurenine pathway:

There is some evidence to suggest that proinflammatory cytokines including TNF alpha induce glial indoleamine dioxygenase (IDO). This activates the kynurenine pathway, thus channelling the available tryptophan to form Kynurenine (Kyn), 3 Hydroxy kynurenine (3HK) and Quinolinic acid (QUIN), rather than the serotonin (5HT). This leads to a decrease in the availability of 5HT, thus contributing to the serotonin hypothesis of depression. Further, 3HK and QUIN are NMDA receptor agonists. High concentrations of these compounds lead to excitotoxicity and calcium mediated cell death. Taken together, there is some data to support the hypothesis that IDO may represent a key player in the pathophysiology of cytokine induced depression.[11]

c. Anti-inflammatory agents have antidepressant properties:

Muller et al, showed that addition of Celecoxib, a cox 2 inhibitor which inhibits prostaglandin E2 to Reboxetine (a norepinephrine reuptake inhibitor), showed significant additional effect on depressive symptoms compared to reboxetine alone. [12] Specific TNF blockade agents have

been shown to improve mood independent of improvement in the inflammatory condition. Tying et al found that 55% of patients with psoriasis who were treated with Etanercept showed a 50% reduction in their Beck's depression inventory (BDI) scores compared to 39% on placebo, an effect-size comparable to that of antidepressants. Analyses of the individual items of the BDI showed that significant improvements at week 12 were seen in feelings of guilt, irritability, anhedonia, sleep, and sexual symptoms. All of them deemed to be core depressive symptoms. They also found that improvement in depression scores did not correlate with improvement in joint pain, skin pain or itching, suggesting that the improvement in mood was independent of improvement in psoriasis. [13]

## II. Serotonergic systems modulates inflammation

### a. Descending serotonergic pathways modulate inflammatory pain

Descending spinal serotonergic pathways from the medulla have been long implicated in the physiology of pain modulation. Zhao et al showed that knockout mice which lacked these descending serotonin pathways in the brain, showed normal thermal and visceral pain responses but were less sensitive to mechanical stimuli and exhibited enhanced inflammatory pain compared with their littermate control mice. More specifically, they showed that the analgesic effect of antidepressants were absent in this strain of mice suggesting that serotonergic pathways play an important role in modulating inflammatory pain, compared to mechanistic pain. [14]

b. Antidepressants have anti-inflammatory and analgesic properties:

Antidepressants with a dual action (inhibiting serotonin and norepinephrine reuptake) have been shown to have analgesic properties and are recommended first line treatments in a number of painful conditions. [15] Tricyclic antidepressants in low doses have been used regularly in rheumatology clinics for their effect on pain, mood and sedation. Antidepressants have also been shown to induce an anti-inflammatory response, independent of its antidepressant action. O'Brien et al showed that CRP levels dropped following treatment with antidepressant. This effect was independent of its antidepressant effect. [16] Vollmar et al found that venlafaxine, significantly decreased clinical symptoms of disease in a murine autoimmune encephalomyelitis model. They showed that Venlafaxine suppressed the generation of pro-inflammatory cytokines IL-12 p40, TNF-alpha and IFN-gamma in encephalitogenic T-cell clones, splenocytes and peritoneal macrophages in vitro. [17] Piletz et al found that raised proinflammatory biomarkers in patients with major depressive disorder showed a decrease in response to treatment with venlafaxine (a mixed serotonin and norepinephrine reuptake inhibitor, exhibiting serotonin reuptake inhibition at lower doses, and norepinephrine reuptake inhibition at higher doses) at the serotonergic dose range rather than the norepinephrine dose range, suggesting that serotonergic pathways mediate anti-inflammatory response to antidepressants. [18] More recently, Sacre et al found that Fluoxetine and Citalopram significantly inhibited disease progression in mice with

CIA. Both drugs were also found to significantly inhibit the spontaneous production of tumor necrosis factor, interleukin-6, and interferon-gamma-inducible protein 10 in human RA synovial membrane cultures. The potential mechanism through which fluoxetine and citalopram treatment exhibited these anti-inflammatory effects was explored. Both the drugs significantly inhibited the signaling of toll like receptors 3, 7, 8, and 9, providing a potential mechanism for their antiinflammatory action. [19] Toll like receptors are proteins thought to mediate innate immunity. They play an important role in initiating an inflammatory reaction in response to pathogen proteins and endogenous molecules found at sites of inflammation and tissue damage.

c. 5HT<sub>2A</sub> receptors mediate inflammatory response to serotonin:

Recent animal and human data suggest that certain subtypes of serotonin receptors may play a role in mediating inflammatory processes. 5-HT<sub>2A</sub> receptors are expressed widely throughout the central nervous system. In the periphery, it is highly expressed in platelets and many cell types of the cardiovascular system, in fibroblasts, and in neurons of the peripheral nervous system. Yu and colleagues found that peripheral activation of 5-HT<sub>2A</sub> receptors in primary aortic smooth muscle cells leads to an extremely potent inhibition of tumor necrosis factor (TNF)-alpha-mediated inflammation, a possible mechanism of action of SSRIs in mediating the anti-inflammatory action. Interestingly they found that proinflammatory markers could also be inhibited by 5HT<sub>2A</sub> stimulation hours after

treatment with TNF-alpha, i.e. after the onset of inflammation. [20] SSRIs including escitalopram are thought to increase extracellular serotonin concentrations at these receptors. However, SSRIs are thought to down-regulate 5HT2A in the long run. Surprisingly blockade of 5HT2A receptors (risperidone) also has the same effect, i.e. down-regulation. This may seem paradoxical. Meyer et al suggested that treatment with SSRIs lead to a decrease in 5HT2A binding potential suggesting a decrease in receptor density over a period of 6 weeks. They found that this decrease in binding potential became less pronounced with increasing age, suggesting that down-regulation of 5HT2A receptors decreased with age. This observation was thought to be due to a possible floor effect caused due to the fact that 5HT2A receptor density decreased with age. Nevertheless, the fact that 5HT2A is down-regulated suggest that SSRIs do have an effect on 5HT2A receptors. The fact that this down-regulation was less in older individuals in Meyer's study means that the 5HT2A stimulation would continue without significant down-regulation, possibly leading to a powerful anti-inflammatory effect peripherally in these individuals, a possible reason why escitalopram had this effect in the individual in the report. [21] Whether this downregulation is essential for the anti-inflammatory effect needs to be investigated further.

In addition, it has been postulated that people on antidepressants that blocked 5HT2A receptors were 45 times more likely to report an adverse drug reaction pertaining to a joint, compared to those that did not block

these receptors. Confirming the hypothesis that 5 HT2A receptors play an important role in mediating inflammatory processes.[22]

## **Conclusion**

In the present case, we see that treatment of comorbid depression with SSRI led to complete remission of arthritis in a 60 year old individual. Postulated mechanisms through which antidepressants possibly mediate this effect include their agonistic action on 5HT2A receptors or by inhibiting the signalling of toll like receptors that are responsible for mediating innate immunity. The relationship between mediators of inflammation and biological substrates of mood seem to be bidirectional. Further studies are required to elucidate the mechanisms involved in this relationship.

## **List of Abbreviations used**

DMARDS - Disease modifying anti-rheumatic drugs

SSRI - Specific serotonin reuptake inhibitor antidepressant

RA - Rheumatoid arthritis

TCA - tricyclic antidepressants

ESR – Erythrocyte sedimentation rate

CRP – C reactive protein

NSAIDs – Non steroidal anti-inflammatory effect

DAS 28 – Disease activity score -28

SERT - Serotonin transporter

TNF- $\alpha$  - Tumour necrosis factor -  $\alpha$

SPECT – Single photon emission tomography

IDO - Indoleamine dioxygenase

Kyn – Kynurenine

3HK - 3 Hydroxy kynurenine

QUIN - Quinolinic acid

5HT - Serotonin

NMDA - N-methyl-D-aspartic acid

BDI - Beck's depression inventory

IL-12 – Interleukin 12

IFN-gamma – Interferon gamma

CIA – Collagen induced arthritis

5HT<sub>2A</sub> – 5HT<sub>2A</sub> subtype of serotonin receptor



## **Consent**

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal

## **Competing interests**

The author(s) declare that they have no competing interests.

## **Author's contributions**

RK was involved in collating the information, review of literature and preparation of the manuscript. RK was involved in collating information regarding the case and getting informed consent from the patient. JC was involved in review of literature and revising the manuscript critically. All authors read and approved the final manuscript.

## **Author's information**

Rajeev Krishnadas MBBS, MD, MRCpsych is a clinical lecturer in psychological medicine at the University of Glasgow. His primary research interests include mood disorder in the medically ill population, primarily patients with inflammatory conditions.

Ranjit Krishnadas MBBS, is a medical graduate with a keen interest in neurology and neuropsychiatry.

Jonathan Cavanagh MBChB, MD, MPhil, MRCPsych is a senior lecturer in psychological medicine and consultant psychiatrist at the University of Glasgow. His research interests include mood disorder in the medically ill population.

### **Acknowledgements**

None

## Reference:

1. Symmons D, Turner G, Webb R, Asten P, Barrett E, Lunt M, Scott D, Silman A: **The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century.** *Rheumatology (Oxford)* 2002, **41**(7):793-800.
2. Malaviya AN, Kapoor SK, Singh RR, Kumar A, Pande I: **Prevalence of rheumatoid arthritis in the adult Indian population.** *Rheumatol Int* 1993, **13**(4):131-134.
3. Deighton C, O'Mahony R, Tosh J, Turner C, Rudolf M: **Management of rheumatoid arthritis: summary of NICE guidance.** *BMJ* 2009, **338**:b702.
4. Dickens C, McGowan L, Clark-Carter D, Creed F: **Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis.** *Psychosom Med* 2002, **64**(1):52-60.
5. Ang DC, Choi H, Kroenke K, Wolfe F: **Comorbid depression is an independent risk factor for mortality in patients with rheumatoid arthritis.** *J Rheumatol* 2005, **32**(6):1013-1019.
6. Aneja R, Grover R, Shankar S, Dhir V, Gupta R, Kumar A: **DAS 28 for defining remission in rheumatoid arthritis in Indian patients.** *Indian Journal of Rheumatology* 2006, **1**(2):48-52.
7. Slaughter JR, Parker JC, Martens MP, Smarr KL, Hewett JE: **Clinical outcomes following a trial of sertraline in rheumatoid arthritis.** *Psychosomatics* 2002, **43**(1):36-41.
8. Baune BT, Eyre H: **Anti-inflammatory effects of antidepressant and atypical antipsychotic medication for the treatment of major depression and comorbid arthritis: a case report.** *J Med Case Reports* 2010, **4**:6.
9. Zhu CB, Blakely RD, Hewlett WA: **The proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha activate serotonin transporters.** *Neuropsychopharmacology* 2006, **31**(10):2121-2131.
10. Cavanagh J, Paterson C, McLean J, Pimlott S, McDonald M, Patterson J, Wyper D, McInnes I: **Tumour necrosis factor blockade mediates altered serotonin transporter availability in rheumatoid arthritis: a clinical, proof-of-concept study.** *Ann Rheum Dis* 2010.
11. Maes M: **The cytokine hypothesis of depression: inflammation, oxidative & nitrosative stress (IO&NS) and leaky gut as new targets for adjunctive treatments in depression.** *Neuro Endocrinol Lett* 2008, **29**(3):287-291.
12. Muller N, Schwarz MJ, Dehning S, Douhe A, Cerovecki A, Goldstein-Muller B, Spellmann I, Hetzel G, Maino K, Kleindienst N *et al*: **The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine.** *Mol Psychiatry* 2006, **11**(7):680-684.
13. Tying S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, Lalla D, Woolley M, Jahreis A, Zitnik R *et al*: **Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial.** *Lancet* 2006, **367**(9504):29-35.
14. Zhao ZQ, Chiechio S, Sun YG, Zhang KH, Zhao CS, Scott M, Johnson RL, Deneris ES, Renner KJ, Gereau RWt *et al*: **Mice lacking central serotonergic neurons show enhanced inflammatory pain and an impaired analgesic response to antidepressant drugs.** *J Neurosci* 2007, **27**(22):6045-6053.
15. Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpaa ML, Kent JL, Krane EJ, Lebel AA, Levy RM *et al*: **Recommendations for the pharmacological**

- management of neuropathic pain: an overview and literature update.** *Mayo Clin Proc* 2010, **85**(3 Suppl):S3-14.
16. O'Brien SM, Scott LV, Dinan TG: **Antidepressant therapy and C-reactive protein levels.** *Br J Psychiatry* 2006, **188**:449-452.
  17. Vollmar P, Nessler S, Kalluri SR, Hartung HP, Hemmer B: **The antidepressant venlafaxine ameliorates murine experimental autoimmune encephalomyelitis by suppression of pro-inflammatory cytokines.** *Int J Neuropsychopharmacol* 2009, **12**(4):525-536.
  18. Piletz JE, Halaris A, Iqbal O, Hoppensteadt D, Fareed J, Zhu H, Sinacore J, Devane CL: **Pro-inflammatory biomarkers in depression: treatment with venlafaxine.** *World J Biol Psychiatry* 2009, **10**(4):313-323.
  19. Sacre S, Medghalchi M, Gregory B, Brennan F, Williams R: **Fluoxetine and citalopram exhibit potent antiinflammatory activity in human and murine models of rheumatoid arthritis and inhibit toll-like receptors.** *Arthritis Rheum* 2010, **62**(3):683-693.
  20. Yu B, Becnel J, Zerfaoui M, Rohatgi R, Boulares AH, Nichols CD: **Serotonin 5-hydroxytryptamine(2A) receptor activation suppresses tumor necrosis factor-alpha-induced inflammation with extraordinary potency.** *J Pharmacol Exp Ther* 2008, **327**(2):316-323.
  21. Meyer JH, Kapur S, Eisfeld B, Brown GM, Houle S, DaSilva J, Wilson AA, Rafi-Tari S, Mayberg HS, Kennedy SH: **The effect of paroxetine on 5-HT(2A) receptors in depression: an [(18)F]setoperone PET imaging study.** *Am J Psychiatry* 2001, **158**(1):78-85.
  22. Kling A, Danell-Boman M, Stenlund H, Dahlqvist R: **Association between the use of serotonin receptor 2A-blocking antidepressants and joint disorders.** *Arthritis Rheum* 2009, **61**(10):1322-1327.