Austin Journal of Orthopedics & Rheumatology

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Case Report

Rheumatoid Arthritis Related Interstitial Lung Disease- Efficacy of Treatment with Intravenous Tocilizumab after Development of Bilateral Lung Thickening- Case Report with 24 Month Follow-Up

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Received: October 26, 2015; **Accepted:** January 15, 2016; **Published:** January 21, 2016

Abstract

Background: The involvement of lung in course of rheumatoid arthritis is very common and is often associated with a poor prognosis. ILD (Interstitial Lung Disease) is often considered as a smoking or drug induced disease, caused by some DMARDs or anti-TNF drugs. Tocilizumab (TCZ) is a biologic agent approved for the treatment of RA.

Case Report: a man, smoker of cigarettes, affected by active and aggressive RA, was treated with Methotrexate (MTX) and low-dose Glucocorticoids (GC) with a good result until he developed a clinical ILD. A higher dose of GC, Azathioprine and Cyclosporin A were not able to get the disease on remission. Therefore we treated the patient with IV monthly TCZ, which suddenly induced the remission of the arthritis, while ILD became more and more severe. The patient was admitted to a Pneumology Unit because of bilateral bronchopneumonia with respiratory failure.TCZ therapy was stopped while respiratory disease reached the complete remission, contrary RA became more and more disabling. Therefore we treated him once more with IV TCZ, reaching the complete remission of RA and ILD. A second minor episode of left pneumonia occurred after further 12 months of therapy with TCZ. The treatment with TCZ was successfully continued after a brief interruption.

24 months of follow-up show that in this patient TCZ is effective on RA and that the flares of the Ra-related ILD become less severe while therapy with TCZ is continued. This case suggests that TCZ, contrary to other drugs, in not contraindicated in the treatment of RA-related ILD.

Keywords: Methotrexate; Glucocorticoids; Tocilizumab; Interstitial lung disease

Background

RA is a systemic disease in which joints involvement is the most common manifestation. It is well known that extra-articular manifestation is present in about 50% of RA patients. Severe extra-articular manifestations are more frequent in course of RA with rheumatoid nodules and are associated with an increased mortality being at an increased risk of developing cardiovascular disease or severe infections [1].

Pulmonary involvement in RA was first described in 1948 by Elmann who reported three cases of extensive pulmonary disease associated with classic manifestations of RA. In two cases autopsy showed a chronic fibrosing type of pneumonitis.

ILD describes a heterogeneous group of parenchymal pulmonary condition. Pulmonary problems, including respiratory infections and lung cancer, are very common in course of RA and contribute to almost 29% of overall mortality [2]. The manifestations of the disease are very varied and can precede the development of joint symptoms and diagnosis of RA; almost all components of the respiratory system can be involved in the systemic inflammatory process of RA: pleuritis, pleurapericarditis, vasculitis, pneumonitis, pulmonary fibrosis, nodulosis [2,3]. ILD is often associated with a poor prognosis. It can be also considered as a drug-induced disease: some DMARDs (in particular MTX and leflunomide), rituximab and anti-TNF drugs are important causes of ILD [4,5].

Several cytokines have been observed to be significantly higer in ILD: the pathogenesis of lung disease and how it may relate to the development of RA include anti-citrullinated-proteins antibodies. The lung can suffer from a loss of immune tolerance and become a large target for autoimmune injury. B cell immunity can contribute to autoimmune ILD after the loss of self tolerance [6].

The incidence of ILD among RA patients is reported with a very different rate (from 5% to 80%), depending on the different population investigated and the different diagnostic methods and criteria. The real incidence is probably around 19%, being one third of these patients asymptomatic [7].

The epidemiology of ILD in course of RA shows that the disease

Citation: Saviola G, Abdi-Ali L, Povino MR, Melchiorre A, Benucci M and Rossini M. Rheumatoid Arthritis Related Interstitial Lung Disease- Efficacy of Treatment with Intravenous Tocilizumab after Development of Bilateral Lung Thickening- Case Report with 24 Month Follow-Up. Austin J Orthopade & Rheumatol. 2016; 3(1): 1025.

Table 1: Rheumatological and respiratory outcomes during treatment with TCZ.

Date	Nov 2012	Dec 2012	Jan 2013	Feb 2013	Jun 2013	Jul 2013	Jun 2014	Jun 2014	Aug 2014	Oct2014
TCZ	1st inf.	2nd inf.	3rd inf.		4th Inf.	5th inf.	17th inf.		18th inf.	20th Inf.
Pain (VAS score)	100/100	50/100	50/100	Admitted In pneumology DPT.	80/100	20/100	60/100	Admitted in pneumology DPT.	80/100	70/100
HAQ score	1.625	0.75	0.125		1.00	0.25	1.00		1.25	1,125
DAS 28 -score	5.78	3.35	2.84		6.63	2.90	2.69		4.72	3.57
Respiratory disease	asymptomatic	asymptomatic	asymptomatic	Bilateral bronchop monia respiratory failure	asymptomatic	asymptomatic	asymptomatic	Left pneumonia	asymptomatic	asymptomatic
DLCO	86%			68%		79%				

is linked to: a) smoking or occupational exposure such as silica exposure b) the duration of RA; c) aging (years)>65; d) the disease activity (CRP and ESR levels); e) anti-CCP and/or Rheumatoid Factor positivity; f) carriage of HLA-DRB1*1502. ILD is more common in male than female patients. In conclusion ILD is a severe complication of severe RA. The interaction between smoking, the lungs and RA is intriguing: citrullination of proteins in the lung is probably caused by smoking with the subsequent development of Anti-Citrulline antibodies [3,8-11].

The diagnosis is made by HRCT scan while plain radiography is often not adequate [8].

Tocilizumab (TCZ) is a biologic agent approved for the treatment of RA acting as an IL-6R blockade. The excessive production of IL-6 has been associated with development of fibrosis and ILD. Therefore the IL-6 inhibition could be an effective way to stop the evolution of ILD [12].

Case Report

A man, 63 year-old, worker in road-yard for 40 years, with exposure to swamp gas, smoker of 40 cigarettes /day till the age of 51. He was affected by active and aggressive RA since the age of 47. He was first treated with different DMARDs, then with Methotrexate (MTX) and low-dose Glucocorticoids (GC) with a good result till 2007 when he developed a clinical ILD. The respiratory complication was proved by a HRCT showing multiple peribronchial, peribronchiolar and parenchymal thickenings associated to ground-glass opacities and pseudonodules. The LUN6 lesions were mostly situated in the inferior lobes, in the lingual and in the right superior lobe. Moreover diffuse interstitial subpleural thickenings were present in the superior lobes. A higher dose of GC, Azathioprine and Cyclosporine A were not able to get a remission of the disease: RA became more and more aggressive causing an important disability. In 2011 a BRONCOSCOPY showed chronic bronchitis with purulent drainage. However, the drainage was negative for bacteria, included tuberculosis and legionella pneumofila; the biopsies confirmed the diagnosis of ILD.

In November 2012 we treated the patient with IV monthly TCZ, at the dose of 560 mg, which suddenly produced the remission of the arthritis, while ILD became more and more severe.

In February 2013 the patient was admitted to a Pneumology Unit because of bilateral bronchopneumonia with respiratory failure. The treatment with TCZ was stopped till the respiratory disease reached the complete remission. Consequently RA had a disabling flare. Therefore, after 4 months where RA became more and more aggressive, we decided to treat the patient once more with TCZ. The patient had a sudden amelioration that lasted for 12 months with remission of RA and ILD as shown by DAS 28 index, DLCO, chest HRCT and X-rays. In June 2014 the patient was once more admitted to a Pneumology Department because of a second minor episode of left pneumonia, without respiratory failure. The treatment with TCZ was stopped for one month, causing a further episode of flare of the arthritis. Therefore in August 2014 we decided to continue the treatment with TCZ. VAS- score for pain evaluation, HAQ score DAS-28score and DLCO of the whole period are reported in (Table 1).

Discussion

As expected TCZ was effective in the treatment of active RA. Moreover the drug was efficacious in the treatment of RA-related ILD. The activity of TCZ in reducing the levels of IL- 6 and IL-17 could explain its efficacy in improving respiratory symptoms. Fibrosis in course of ILD has been reported to be associated to excessive production of IL-6 [12].

The possible efficacy of TCZ in RA related ILD is discussed in the literature. A case of fatal ILD has been reported by Kawashiri [13]. He described a patient who had been a smoker of 30 cigarettes for 40 years, affected by a chronic respiratory failure in chronic treatment with domestic oxygen therapy. Moreover the patient described by Kawashiri had been previously treated with etanercept for 30 months

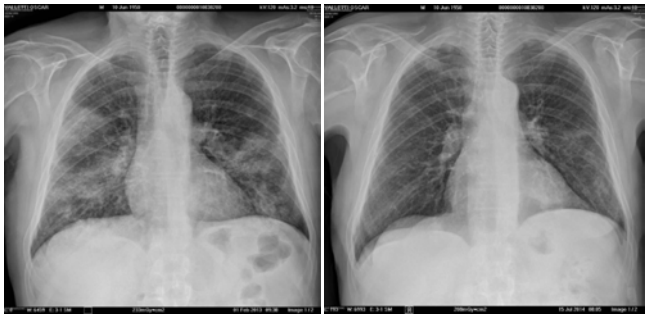

Figure 1: Chest X-rays at the beginning of the treatment with TCZ compared with chest X-rays after 10 months with TCZ treatment.

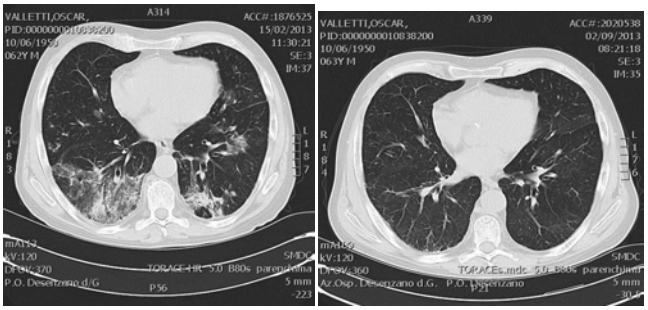

Figure 2: HRCT at the beginning of the treatment with TCZ and after 10 months.

with worsening of the arthritis and therefore switched to TCZ. In that case the new therapy had only a moderate improvement on RA symptoms, but after 10 months of therapy with TCZ the patient died because of an acute respiratory exacerbation [12]. By contrary Mohr described a patient affected by RA-ILD where the treatment with TCZ obtained an improvement both in respiratory (alveolitis and ground-glass opacities) and arthritis symptoms [14]. More recently Keidel published of a 15 year old girl affected by an ILD in course of an undifferentiated auto inflammatory disorder partially responsive to anakinra [15]. The switch to TCZ obtained a satisfying result [12]. Finally JUSTET successfully treated refractory organizing pneumonia associated with Sjogren's disease [16].

Conclusion

In this case-report with 24-month follow-up, TCZ was effective in the treatment of RA and RA- related ILD with an evident amelioration of the respiratory disease. This case seems to show that TCZ, contrary to anti-TNF drugs, is not contraindicated in the treatment of RA-related ILD. Further study involving a large number of patients is needed to confirm this hypothesis.

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Austin J Orthopade & Rheumatol - Volume 3 Issue 1 - 2016
ISSN: 2472-369X | www.austinpublishinggroup.com

Citation: Saviola G, Abdi-Ali L, Povino MR, Melchiorre A, Benucci M and Rossini M. Rheumatoid Arthritis Related Interstitial Lung Disease- Efficacy of Treatment with Intravenous Tocilizumab after Development of Bilateral Lung Thickening- Case Report with 24 Month Follow-Up. Austin J Orthopade & Rheumatol. 2016; 3(1): 1025.