CASE REPORT

Pneumocystis jiroveci pneumonia in a patient taking Benepali for rheumatoid arthritis

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SUMMARY

We present a case of a 57-year-old woman who contracted *Pneumocystis jiroveci* pneumonia while on Benepali, the biosimilar version of etanercept for rheumatoid arthritis. She had seropositive erosive disease. She was admitted to clinic with a 2-week history of dyspnoea, dry cough and fever. Her initial examination showed her to be hypoxic on air with saturations of 77% and left basal crackles. Her admission chest X-ray showed fine reticular shadowing, with an initial suspicion of pulmonary fibrosis. She was empirically treated for community-acquired pneumonia but continued to deteriorate with a worsening type 1 respiratory failure. She was intubated and ventilated on intensive care. The suspicion was raised of *P. jiroveci* pneumonia given her immunosuppression, hypoxic presentation and chest X-ray changes. This was confirmed on sputum PCR. She was treated with a 3-week course of steroids and co-trimoxazole. She was discharged home after a 2-week admission.

BACKGROUND

The use of biologic drugs in rheumatoid arthritis is increasingly more common¹ and many patients present to the acute medical take while on these medications.

Though uncommon, the risk of opportunist infection such as tuberculosis, herpes zoster and *Pneumocystis jiroveci* pneumonia is well documented on antitumour necrosis factor (TNF) biologic drugs such as infliximab and etanercept.^{2,3}

Biosimilar drugs were licensed for use in February 2015 for rheumatoid arthritis.^{4,5} The two most commonly used ones are Benepali (biosimilar to etanercept) and remsima (biosimilar to infliximab).

There have been no published case reports of *P. jiroveci* pneumonia in patients on Benepali.

Most general physicians are aware of the possibility of *P. jiroveci* pneumonia when reviewing patients with HIV⁶; however, it is important to be aware of this in all immunosuppressed patients, including those on biologic treatment including biosimilar drugs for rheumatoid arthritis.

We present a case of a 57-year-old woman with *P. jiroveci* pneumonia while on Benepali for rheumatoid arthritis.

CASE PRESENTATION

A 57-year-old woman presented to clinic with progressive dyspnoea over a 2-week period.

She had a background of seropositive erosive rheumatoid arthritis diagnosed in 2007. She had been previously treated with abatacept, tocilizumab, rituximab and certolizumab. Since April 2017, she had been on Benepali 50 mg once weekly subcutaneously in combination with methotrexate 12.5 mg weekly.

On presentation to clinic, she gave a 2-week history of progressive dyspnoea and dry cough, intermittent fever and fatigue. She was concerned about having contracted an infection so stopped her methotrexate and Benepali accordingly.

On examination, she was hypoxic with saturations of 77% on air, and afebrile with a heart rate of 80 beats per minute. She had crackles at the left base on examination of her chest. She was admitted to the acute receiving unit.

She was a current smoker with no other significant medical history or family history. She was retired and lived with her husband and children.

She was treated on the ward for 36 hours but had an increasing oxygen requirement and was transferred to the intensive care unit (ICU) for intubation and ventilation.

INVESTIGATIONS**Imaging**

Her admission chest X-ray showed fine reticular shadowing predominantly affecting the mid lower zones bilaterally (figure 1). Appearances were reported as suspicious of pulmonary fibrosis with no convincing evidence of consolidation.

CT thorax was undertaken (high-resolution CT was not possible because she was ventilated). This showed multifocal inflammatory change, severe emphysema and no established interstitial fibrosis (figure 2). There was evidence of diffuse

Figure 1 Admission chest X-ray showing fine reticular shadowing predominantly affecting the mid lower zones bilaterally.

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Figure 2 CT thorax showing multifocal inflammatory change, severe emphysema and no established interstitial fibrosis.

ground-glass change possibly due to viral pneumonitis, cardiac failure/fluid overload or less likely methotrexate-related pneumonitis or hypersensitivity pneumonitis.

Subsequent high-resolution CT chest on discharge showed almost complete resolution of the inflammatory changes with background emphysema (figure 3).

Microbiology and virology

Her sputum PCR confirmed a diagnosis of *P. jiroveci* pneumonia. Influenza, legionella, respiratory viral PCR, blood cultures and blood borne virus screen of hepatitis B, C and HIV were all negative.

Blood samples

On admission, full blood count showed white cell count 9.8, lymphocytes 2.1, neutrophils 6.5, platelets 548, C-reactive protein (CRP) 165, normal urea and electrolytes and liver

Figure 3 High-resolution CT showing almost complete resolution of the inflammatory changes with background emphysema.

function tests. Her CRP continued to climb, peaking at 267 and falling after treatment to 43.

Her admission arterial blood gas showed a PO_2 of 7.4 on 35% oxygen, with a normal CO_2 , no acidosis and a lactate of 0.9.

Her arterial blood gas before admission to ICU showed a PO_2 of 6.0 on 10 L oxygen, with H^+ of 38.2 and a PCO_2 of 5.0.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included community-acquired pneumonia (bacterial or viral), mycobacterium tuberculosis (known to be increased in patients on anti-TNF therapy), methotrexate pneumonitis and methotrexate-induced interstitial lung disease. The images were reviewed by a consultant radiologist and consultant respiratory physician with a specialist interest in interstitial lung disease and felt not to be consistent with either of these diagnoses. Also, the patient had been taking methotrexate for over 10 years, making methotrexate-induced pneumonitis less likely as it tends to occur in the first year of commencing the drug.⁷

The suspicion was raised of *P. jiroveci* pneumonia given her immunosuppression, hypoxic presentation and chest X-ray changes. This was confirmed on sputum PCR.

TREATMENT

The patient was treated initially with empirical antibiotic therapy consisting of amoxicillin 1g three times a day and clarithromycin 500mg twice daily to cover community-acquired pneumonia. When she was transferred to the ICU, her treatment was escalated to include intravenous methylprednisolone 30mg twice daily intravenously and co-trimoxazole 1920 mg four times a day to treat suspected *P. jiroveci* pneumonia.

OUTCOME AND FOLLOW-UP

The patient was successfully treated for *P. jiroveci* pneumonia. She spent 8 days in intensive care and was ventilated for four of those days.

She completed a 3-week course of co-trimoxazole and continued on prednisone 10mg once daily until her review in rheumatology clinic.

During outpatient follow-up, she was restarted on methotrexate at 10mg weekly and was being considered for further therapy in the form of tofacitinib, a Janus kinase inhibitor.

DISCUSSION

Biosimilar medications

This case demonstrates a rare opportunistic infection in a patient on Benepali, which is considered a safe drug for use in rheumatoid arthritis.⁴

The use of biologic drugs in rheumatoid arthritis is becoming increasingly common¹ and many patients present to the acute medical take while on these medications.

Currently, there are five available TNF inhibitors licensed for use in rheumatoid arthritis. These are adalimumab, certolizumab pegol, etanercept, golimumab and infliximab.

Biosimilars are biopharmaceuticals assessed by regulatory agencies to have efficacy and safety similar to their reference products. They were introduced to the UK market in February 2015 for the treatment of rheumatoid arthritis. Most research on biosimilars has been done in the context of clinical trials, but real-world data are lacking.⁵ The two most commonly used agents are Benepali (biosimilar to etanercept) and remsima (biosimilar to infliximab).

Although these medications are found to have similar safety and efficacy during testing,⁴ there have been no published case reports of *P. jiroveci* pneumonia in patients on Benepali. It is important to note the efficacy end points focused on improvement in American College of Rheumatology 70 response criteria and Disease Activity Score 28 and the safety data does not specifically mention opportunistic infections.⁴

Risk of *P. jiroveci* pneumonia in patients taking etanercept

Etanercept was first used for rheumatoid arthritis in 2001. Updated data from the British Society for Rheumatology Biologics Register for rheumatoid arthritis showed the incidence rate of opportunistic infections was low at 1.33 cases per 1000 patient years.⁸ The authors looked at 19 162 patients and included patients who were either on anti-TNF therapy, rituximab or tocilizumab. Of the opportunistic infections documented, there were 12/106 cases of *P. jiroveci* pneumonia in patients on anti-TNF therapy and 8/24 cases in those on rituximab.

A meta-analysis of biologic therapies in rheumatoid arthritis and the risk of opportunistic infections published in clinical infectious disease in 2014 showed no statistically significant difference in *P. jiroveci* infection rates between patients on biologics and the control group.⁹ The authors, however, observe that infection rates and mortality data implied an association with biologic therapy that does not reach statistical significance.⁹

The authors also mentioned that large registries are needed to gather and further analyse the data on these rare opportunistic infections.⁹

Postmarketing surveillance reports by the Japan College of Rheumatology indicated a high incidence of *P. jiroveci* pneumonia in patients with rheumatoid arthritis receiving the anti-TNF agents infliximab (0.4% of 5000 patients), etanercept (0.2% of 7091 patients) and adalimumab (0.3% of 3000 patients).¹⁰ The mortality of *P. jiroveci* pneumonia with etanercept use was 18.5%. It is important to note that the incidence of *P. jiroveci* pneumonia is higher in Japan than western countries.³

Other risk factors for *P. jiroveci* pneumonia

An association of *P. jiroveci* pneumonia with pre-existing lung disease has also been reported for patients with rheumatoid arthritis.¹¹ Our patient had pre-existing emphysema.

A retrospective case study in Japan in 2017 looking at all cases of *P. jiroveci* pneumonia from 2009 to 2013 showed that significant risk factors for *P. jiroveci* pneumonia were having underlying lung disease, use of corticosteroids, use of biologics and use of methotrexate. Lymphopenia also increases the risk of developing *P. jiroveci* pneumonia. Our patient had not received oral prednisolone for 3 years prior to developing *P. jiroveci* pneumonia, nor was she lymphopenic. The study also listed male sex and age >70, both of which did not apply to our patient.

A retrospective review of 15 case studies of *P. jiroveci* pneumonia associated with etanercept treatment in rheumatoid arthritis showed the infection developed within 26 weeks following the first injection of etanercept in 86.7% of the patients.¹¹ Our patient had been taking Benepali for 29 weeks but was unwell for 2 weeks prior to this.

All patients suffering from *P. jiroveci* pneumonia presented with a rapid and severe clinical course and the overall mortality was 6.7%. All 15 patients who received etanercept in this study showed acute-onset *P. jiroveci* pneumonia and severe hypoxaemia or requirement for oxygen therapy.¹¹ This is again similar to our case.

There is a link between *P. jiroveci* pneumonia developing post-rituximab¹²; however, it is important to note our patient had a 6-month washout period from finishing treatment with rituximab and starting Benepali.

Most studies indicate better survival rates for patients with HIV-positive *P. jiroveci* pneumonia (86%–92%) than for patients with HIV-negative *P. jiroveci* pneumonia with various underlying conditions (51%–80%).¹³

Relationship of above data to this case and Benepali

In a 52-week results of the phase 3 randomised study comparing SB4 (Benepali) with reference to etanercept in patients with active rheumatoid arthritis, there were no reported cases of *P. jiroveci* pneumonia.⁴

The above data shows that *P. jiroveci* pneumonia is an opportunistic infection that can occur rarely in patients on etanercept, and when it does there is a risk of mortality. There are so far no other documented cases of *P. jiroveci* pneumonia in Benepali, the biosimilar to etanercept.

In conclusion, *P. jiroveci* pneumonia in immunosuppressed rheumatoid patients on biologic therapy has a high mortality rate. It is therefore important to have a high index of suspicion for this condition in patients who are taking biologic drugs and to have an awareness of what these drugs are, as well as the biosimilar versions that patients may present on.

Learning points

- ▶ *Pneumocystis jiroveci* pneumonia is an opportunistic infection that presents in patients who are chronically immunosuppressed and has an associated increased mortality.
- ▶ The use of biologic drugs are becoming increasingly more common in patients with rheumatoid arthritis, including biosimilar versions such as Benepali, and it is important to remember to consider opportunistic infections in these patients, especially if they do not respond to initial antibiotic therapy.
- ▶ Clinicians must have a high index of suspicion for *P. jiroveci* pneumonia and other opportunistic infections when reviewing these patients, especially if they present with interstitial chest X-ray changes and severe hypoxia.

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