Safety and Efficacy of Infliximab in Primary Biliary Cirrhosis Associated with Rheumatoid Arthritis

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Received date: July 24, 2017, Accepted date: August 26, 2017, Published date: August 31, 2017

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**Abstract**

**Background:** Primary biliary cirrhosis (PBC) is an autoimmune disease. Implication of TNF alpha in its pathogenesis has been suggested.

**Findings:** We describe the case of a 56-year-old female patient with rheumatoid arthritis (RA) treated with anti-TNF alpha agents (Infliximab). During this treatment, perturbation of liver tests was noted. Investigations concluded to PBC. Ursodeoxycholic acid was prescribed in association with infliximab. This therapy maintained liver enzymes within the normal range with good response of the RA.

**Conclusions:** This case suggests that TNF alpha blockers may be a good therapeutic alternative when PBC is associated to Rheumatoid Arthritis.

**Keywords:** Rheumatoid arthritis; Primary biliary cirrhosis; Tumor necrosis factor; Alpha blockers

**Background**

Primary biliary cirrhosis (PBC) is a chronic, progressive, cholestatic liver disease characterized by non-suppurative destruction of septal and smaller intralobular bile ducts and portal inflammation resulting in fibrosis and eventual cirrhosis [1]. PBC and Rheumatoid Arthritis (RA) are both autoimmune disorders and their association is rarely described in the literature [2].

These two diseases share a common auto-immune ground: The pro-inflammatory tumor necrosis factor alpha (TNF alpha) cytokine had been involved in their physiopathology. Herein, we report a rare case of RA associated with PBC which was successfully treated with TNF alpha blockers.

**Case report**

This case report referred to a 56-year-old woman, presented in our department with five years evolving symmetrical polyarthritis involving large and small joints. Immunological investigations (rheumatoid factor, antibodies to citrullinated peptides (ACPA) and antinuclear antibodies) were negative. Plain radiographs revealed typical bilateral erosion of the metacarpophalangeal joints. The patient was diagnosed with RA, according to the American Rheumatism criteria of 1987 [3]. She was first treated with methotrexate (MTX), initially at 10mg/week. However, her disease was still in flare despite the increase of MTX doses to 20 mg/week, in association with low-dose corticosteroids. Due to her sustained high disease activity, as attested by the Disease activity score DAS28 at 6.4, Infliximab (3 mg/kg at weeks 0, 2, 6 and thereafter every 8 weeks) was started, in association with MTX (10 mg weekly) with good clinical and biological response.

After the 7th infusion, the laboratory findings showed abnormal liver function tests: alanine aminotransferase (ALT) at 59 U/L (normal range: 8-53), aspartate aminotransferase (AST) at 44 U/L (normal range: 5-40), alkaline phosphatase (AP) at 400 U/L (normal range: 40-120) and g-glutamyltransferase (GGT) at 303 U/L (normal range: 5-50). Both MTX and infliximab were stopped with no further normalization of liver tests. Viral markers for hepatitis B and C were negative. Liver ultrasound was normal showing no biliary duct dilatation and no biliary sludge. Mitochondrial antibodies (AMA M2 type) were positive at a rate of 1/400. Liver biopsies were then conducted and have confirmed the diagnosis of PBC (stage I of Sheuer). Ursodeoxycholic acid (Ursolvan) was initiated at a dose of 600mg daily with initial good liver function normalization. Six months later, and because of a flare of the RA, TNF inhibitors and MTX were restarted at the same doses, in association with 10mg/day of corticosteroids. After 6 months of treatment with Ursolvan and at the 10th infliximab infusion, the RA remained uncontrolled (DAS 28 at 5.84) and the cholestasis was still persistant (ALP 273 IU/l). This leaded to increase doses of infliximab at 5 mg/kg. The outcome was favorable on both hepatic and osteoarticular diseases with a current decline of 5 years and a total of 34 infusions received to date.

Table 1 summarizes the parameters of RA activity and the various biological controls throughout evolution.
The pathogenesis of the PBC is partially unresolved. Among factors incriminated, TNF alpha had been mentioned in view of its hepatic expression in many liver dysfunctions including PBC [6,9]. This cytokine had shown to increase transforming growth factor beta (TGF beta) production and seems to be implicated in the pathogenesis of fibrogenesis [10]. Indeed, TNF alpha was the most abundant cytokine, following by TGF beta in the bile duct epithelial cells in patients with PBC [11,12]. Moreover, serum levels of TNF alpha may reflect the severity of histological liver changes [13]. Regarding the latest aspect, studies aiming to identify gene's susceptibility to PBC have showed a significant association with TNF alpha promoter region polymorphism at position 308, which increases TNF alpha expression and disease severity [14]. Overall, these findings demonstrate an outstanding role of TNF alpha in PBC pathogenesis, suggesting that anti-TNF alpha agent, used for treating most inflammatory rheumatic conditions, may result in a positive response in patients with PBC [15].

To our knowledge, few descriptions of successful treatment of the concurrence of PBC and RA with TNF blockers had been reported [15]. Furthermore, a serum level of TNF alpha seems to reflect the severity of liver morphological changes [16]. Overall, the prominent role of TNF alpha in PBC pathogenesis is highlighted in recent literature, suggesting that anti-TNF alpha treatment, currently used for most inflammatory rheumatic conditions, may account for a successful response also in PBC. Spadaro et al. [15] have reported a similar case of overlapping RA and PBC with efficient treatment with Etanercept after resistance to Infliximab. It is likely that differences in drug characteristics [dosing, pharmacokinetics, immunogenicity, ability to block lymphotoxin alpha (LT alpha) and fix complement, capacity to induce apoptosis] and patients genetic predisposition shaped the treatment outcome and represent a potential explanation for some of the observed disparities in efficacy profiles [17] as in your case, when the patient developed abnormal liver function after 7th dose INF at a dose of (3 mg/kg) then responded to a higher dose of INF treatment (5 mg/kg).

In conclusion, our case showed that TNF blockers maintained liver enzymes within the normal range and controlled the arthritis with a decline of 60 months. Moreover it suggests that infliximab is considered to have a beneficial potential on the treatment of overlapping RA and PBC. Additional studies may be considered to better explore the therapeutic role (dosage and molecule disparities) of TNF blockers on clinical and morphological course of PBC associated with RA.

References


Table 1: summarizes the parameters of RA activity and the various biological controls.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before blockers Initiation</th>
<th>TNF 7th infunsk</th>
<th>10th infusion INF: (3mg/kg ) At 6 months of Ursolvan 600 mg/d</th>
<th>12th infusion INF (5mg/kg )</th>
<th>34th perfusion INF (5mg/kg )</th>
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<td>5.84</td>
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