

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

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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. Ursodesoxicholic 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 Rheumatology 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 persistent (ALP 273 IU/l). This led 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.

Variable	Before TNF blockers initiation	7th infusion of INF (3mg/kg)	10th infusion INF: (3mg/kg)	12th infusion INF (5mg/kg)	34th perfusion INF (5mg/kg)
			At 6 months of Ursolvan 600 mg/d)		
DAS 28	5.58	4.2	5.84	3.6	3.5
TJ/SJ	15-May	2/0	06-Apr	02-Jan	02-Jan
HAQ	2.5	1.62	1.62	1	1.37
CRP	20	6	12	21	30
ESR	40	28	65	27	40
ALP	198	400	273	120	128
GGT	30	303	47	39	40
AST	21	44	16	30	16
ALT	24	59	15	32	19

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

INF: Infliximab; **DAS 28:** Disease activity score (28 joints); **TJ/SJ:** Tender joints/swollen joints; **HAQ:** Health assessment questionnaire; **CRP:** C-reactive protein; **ESR:** Erythrocyte sedimentation rate; **APL:** Alkaline phosphatase; **GGT:** G-glutamyltransferase; **AST:** aspartate aminotransferase; **ALT:** Alanine aminotransferase

Discussion

PBC and RA are chronic diseases in which autoimmune features prevail, although the exact physiopathology of both conditions is still unclear [2]. This case report illustrates firstly the emergence of PBC in the course of erosive RA which is very uncommon. Then, it raises the therapeutic challenges of such association. Currently, there is no exact estimation of PBC prevalence in RA patients but some studies estimated that 10-18% of RA patients have antimitochondrial antibodies (AMA), which have a demonstrated association with PBC. Furthermore, about 50% of patients with PBC become rheumatoid factor positive during the course of the disease [4,5] and this positivity rate could reach 70% in some studies [6]. According to Koga et al. anti-citrullinated protein antibody (ACPA) are found in 2.7% of the CPB patients in case of association with RA [7]. Santiago et al. showed that ACPA (third generation) were present in 3.7% of the PBC patients, independently of the association with RA [8].

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, followed 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.

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