# Infliximab: a Promising Alternative Therapy for Refractory Arthritis/Urethritis/Conjunctivitis Triad

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Arthritis-urethritis-conjunctivitis, the AUC triad, is commonly known as Reiter's disease. The diagnosis of this specific subtype of reactive arthritis is based on the presence of conjunctivitis, urethritis and asymmetric arthritis, with a limited course. In some patients, attacks never subside completely and instead trigger a severe and refractory inflammatory disease. Classically, treatment is indicated according to disease stage. First-line drugs include non-steroidal anti-inflammatory drugs and antibiotics if there is evidence of infection; for chronic or refractory disease, sulfasalazine, methotrexate and other immunomodulators are prescribed [1-3].

Tumor necrosis factor-alpha antagonists have emerged as a potential alternative for the treatment of various rheumatic conditions, including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and juvenile idiopatic arthritis, as this cytokine is known to play a prominent role in inflammation. Blockage of TNFα has changed the natural history of rheumatoid arthritis and ankylosing spondylitis, but the use of TNFα blockers in the AUC triad has only been described in two patients [4,5]. One patient presented with the AUC triad associated with human immunodeficiency virus and demonstrated a resolution of symptoms that lasted four times longer than the second, conventional, case, suggesting that the latter may have experienced a more prompt response [4].

We present three patients with refractory AUC triad not associated with HIV infection, who were treated successfully with infliximab and have the longest follow-up described to date.

TNFα = tumor necrosis factor-alpha

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## PATIENT DESCRIPTIONS

### PATIENT 1

In 1997 a 34 year old white man experienced inflamed swelling of the left wrist and knee joints for about 3 weeks, along with pain over his heel tendons (enthesitis). He also had genital lesions with sharply delimited erosions of the glans that were consistent with circinate balanitis and erythematosquamous papules on his soles consistent with keratoderma blennorrhagica. Subsequently, he noticed dysuria and a clear urethral discharge associated with conjunctivitis. He was sexually active and had no history of sexually transmitted diseases. He denied any recent infections. Antinuclear antibodies, rheumatoid factor, HIV, syphilis and hepatitis B and C serologies were all negative. His HLA-B27 was positive. Urethral discharge cultures were negative for Gonococcus and Chlamydia. X-rays of his knees and ankles were unremarkable. He was initially treated with NSAIDs , prednisone (10 mg/day) and sulfasalazine (3 g/day). Subsequently, methotrexate (20 mg/week), cyclosporine (200 mg/day) and intramuscular betamethasone were added due to the severity of the symptoms. After 3 months, cyclosporine was withdrawn, and infliximab was instituted (3 mg/kg/dose) as the skin lesions had deteriorated and the arthritis had not subsided. A complete resolution of both symptoms was attained after the second dose of infliximab. The patient's white blood cell count decreased from 9390/mm$^3$ (measured one week before initiation of infliximab) to 5950/mm$^3$ (measured after the second infliximab infusion), while his platelet count decreased from 359,000 to 222,000/mm$^3$, his erythrocyte sedimentation rate decreased from 33 to 2 mm/hour and his C-reactive protein decreased from 34.8 to 3.73 µg/L. Prednisone and sulfasalazine were tapered and stopped after the third dose of infliximab. Methotrexate was tapered to 12.5 mg/week. He has received 15 doses of infliximab and remains in remission.

### PATIENT 2

In 1979, a 47 year old white man had conjunctivitis, arthritis involving the right knee and ankle joints, enthesitis, dermatological lesions consistent with keratoderma blennorrhagica, and

AUC = arthritis-urethritis-conjunctivitis
HIV = human immunodeficiency virus

NSAID = non-steroidal anti-inflammatory drug

**Table 1.** Demographic and clinical features of the three cases with the AUC triad

| | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| **Age (yrs)** | 34 | 47 | 56 |
| Age at presentation | 24 | 19 | 37 |
| Gender | Male | Male | Male |
| Disease duration | 10 yrs | 28 yrs | 19 yrs |
| Race | White | White | White |
| Urethritis | + | + | + |
| Conjunctivitis | + | + (and uveitis) | + (and uveitis) |
| Peripheral arthritis | + | + | + |
| Axial involvement | - | - | - |
| Enthesitis | + | + | + |
| Circinate balanitis | + | + | - |
| Keratoderma blennorrhagica | + | + | - |
| HLA-B27 | + | + | - |
| Previous treatment | NSAIDs prednisone methotrexate Sulfasalazine Cyclosporine | NSAIDs Methotrexate Sulfasalazine Chloroquine | NSAIDs prednisone Pethotrexate Sulfasalazine Cyclosporine Azathioprine Leflunomide |
| Anti-TNF | Infliximab 3 mg/kg | Infliximab 5 mg/kg | Infliximab 5 mg/kg |
| No. of infusions (total) | 17 | 5 | 7 |
| No. of infusions needed to achieve a clinical response | 2 | 3 | 3 |

circinate balanitis associated with clear penile discharge. He also had a 4 week history of diarrhea that preceded the onset of these symptoms. He reported several episodes of uveitis with consequent amaurosis on the right eye. ANA, RF, HIV, syphilis and hepatitis B and C serologies were negative. His HLA-B27 was positive. Urethral discharge cultures were negative for Gonococcus and Chlamydia. The patient was treated with NSAIDs, prednisone (10 mg/day), chloroquine (250 mg/day), sulfasalazine (3 g/day), and methotrexate (20 mg/week) for decades, without a satisfactory clinical remission. Infliximab therapy was started (5 mg/kg/dose), and a clear improvement in the arthritis symptoms was seen after the first dose, while a complete resolution of skin lesions was achieved after the third dose. His WBC count decreased from 7160/mm$^3$ (measured before the first infusion) to 4420/mm$^3$ (measured after the third infliximab administration), and platelet count decreased from 397,000 to 262,000/mm$^3$. Both ESR and CRP were also decreased, from 111 to 7 mm/hr and 75 to 1.99 μg/L, respectively. He has received his fifth dose of infliximab and has been able to discontinue corticosteroids, chloroquine and methotrexate.

ANA = antinuclear antibodies
RF = rheumatoid factor
WBC = white blood cell

#### PATIENT 3

A 57 year old white man presented with a 19 year history of urethritis, conjunctivitis, asymmetrical polyarthritis of large joints, and enthesitis. He also related a history of two episodes of uveitis. Serologies for hepatitis B and C, HIV and syphilis were negative. He denied any recent infections. His HLA-B27 was negative. He had been treated with different combinations of NSAIDs, methotrexate, sulfasalazine, chloroquine, azathioprine, leflunomide and prednisone (20 mg/day). However, swelling of the large joints, along with limited range of motion and severe debilitating pain, persisted. Infliximab therapy (5 mg/kg/dose) was initiated. His ESR decreased from 37 mm/hr before infliximab to 7 mm/hr after treatment initiation, and CRP decreased from 18 to 4.9 μg/L. Resolution of the arthritis was achieved after the third dose. He has now received seven doses of infliximab, and methotrexate, chloroquine, azathioprine, sulfasalazine and prednisone were tapered and have now been discontinued. The main characteristics of the three cases are summarized in Table 1.

ESR = erythrocyte sedimentation rate
CRP = C-reactive protein

## COMMENT

Anti-TN-α blocking agents seem to represent a new therapeutic option for refractory AUC triad cases and can achieve a persistent satisfactory response. The rationale for targeting TNFα in the AUC triad comes from studies of patients with spondyloarthropathies and reactive arthritis, in which the role of TNFα in the molecular mechanisms underlying or perpetuating these inflammatory processes has been demonstrated. With regard to spondyloarthropathies, TNFα inhibition resulted in rapid amelioration of clinical symptoms and continued clinical benefits. In addition, TNFα is also elevated in synovial fluid and skin lesions of patients with psoriatic arthritis. Of interest, high serum levels of TNFα have been detected in chronic patients with reactive arthritis.

Disease duration does not seem to be a limiting factor regarding response to therapy in the AUC triad, as rapid improvement was observed despite a very long disease duration in all three patients reported here. In addition, we provided evidence that among AUC triad patients, high and persistent lev-

els of CRP may indicate a more responsive disease since we observed a rapid decrease after the initiation of anti-TNF therapy [3].

The suggested initial dose of infliximab treatment is higher for ankylosing spondylitis than for rheumatoid arthritis. We obtained satisfactory responses with both doses. In the HIV-associated case the response was prolonged [4]. However, as this latter condition is usually more refractory to treatment, we speculate that the lower dose may have contributed to the extended time needed to achieve remission.

The present report suggests that TNFα plays a role in the pathogenesis of refractory AUC triad without associated infection. The preliminary effect of infliximab reported here raises the intriguing possibility that the targeting of this cytokine might represent a new therapeutic option offering rapid and persistent responses in this potentially debilitating disease.

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