Pediatr Nephrol (2004) 19:1281–1284
DOI 10.1007/s00467-004-1573-2

BRIEF REPORT

David Raveh · Ovadia Shemesh · Yaakov Jack Ashkenazi · Robert Winkler · Vivian Barak

Tumor necrosis factor-α blocking agent as a treatment for nephrotic syndrome

Received: 8 April 2003 / Revised: 11 April 2003 / Accepted: 12 May 2004 / Published online: 25 August 2004

Abstract We report a 13-year-old boy with refractory nephrotic syndrome (minimal change with mesangial proliferation) who failed the standard treatment protocols. There was some temporary response to large steroid doses, but even the Mendoza protocol could not induce remission. We show suppression of the proteinuria with Infliximab (Remicade) with tapering of steroids. Serial serum levels of tumor necrosis factor (TNF)-α are shown and discussed. We suggest studying the TNF-α blocking agents as optional treatment for nephrotic syndrome.

Keywords Nephrotic syndrome · Tumor necrosis factor-α

Introduction

Current treatment protocols for idiopathic nephrotic syndrome traditionally include glucocorticosteroids as the cornerstone, while concomitant drugs are added in relapsing or refractory cases, or as steroid-sparing agents. These drugs include cyclophosphamide, cyclosporin A, tacrolimus (FK-506), and mycophenolate mofetil (MMF). These drugs, administered for a long time in refractory or relapsing cases, could lead to a wide range of serious adverse effects: from the known steroid side effects to immunosuppression, inherent nephrotoxicity, B-cell lymphoma, and others. Recent data have suggested a role for tumor necrosis factor (TNF)-α in nephrotic syndrome. For example, serum TNF-α levels are elevated in nephrotic syndrome and normalize with remission of disease [1, 2, 3, 4, 5, 6, 7]. TNF-α is suggested to cause proteinuria based on a laboratory model, and anti-TNFα agents can control the proteinuria. We report a child with nephrotic syndrome refractory to standard therapy who responded to a TNF-α blocking agent.

Editorial comment. Before the decision was made to accept this report for publication, it was carefully considered by both medical and ethical experts with special regard for the acknowledged relationship between the patient and one of the treating physicians. We believe that this "hypothesis paper" may be of interest to our readership.

D. Raveh · O. Shemesh · Y. J. Ashkenazi · R. Winkler
Division of Internal Medicine,
Shaare Zedek Medical Center,
Jerusalem, Israel

V. Barak
Immunology Laboratory, Oncology Department,
Hadassah Medical Center,
Jerusalem, Israel

D. Raveh (✉)
Infectious Disease Unit,
Shaare Zedek Medical Center,
Jerusalem, Israel
e-mail: ravehmed@hotmail.com
Fax: +972-2-6666342

Case report

A 13-year-old boy, previously healthy, was hospitalized on November 1999 for nephrotic syndrome. In the weeks prior to admission there was no obvious acute viral illness and he gradually developed weakness and pitting ankle edema. Blood pressure reached 160/100 mmHg. The highest proteinuria reached 25 g/day; the highest total cholesterol was 480 mg/dl. Urine dipstick was positive 2+ for red blood cells, but urine microscopy was negative for any cells or casts. Hypermagnesemia and mild elevation of lactic dehydrogenase were also detected. Kidney biopsy showed minimal change with mesangial proliferation. Immunohistochemistry was negative. Serological blood tests for autoimmune and infectious diseases were negative, and a diagnosis of idiopathic nephrotic syndrome was made.

His treatment protocols over the 5 years are described here and shown in Fig. 1. The initial treatment (over 5 months) included five doses of 1 g methylprednisolone each, followed by 80 mg oral prednisone daily (1.6 mg/kg per day). After 8 weeks the proteinuria decreased to 170 mg/day. However, severe bilateral knee pains and effusion developed, and bone scan and magnetic resonance imaging were suggestive of early osteonecrosis. The steroid treatment was switched to alternate day, with resolution of the knee problem but with a relapse of proteinuria in 10 days to 4,000 mg/day. The second treatment protocol (over 6 months) included seven monthly doses of IV cyclophosphamide [8] in a cumulative dose of 7.2 g (body surface area=1.55 m^2), with oral prednisone (70 mg tapered to 25 mg every other day). The proteinuria was unaffected (Fig. 1), so the seventh planned dose was

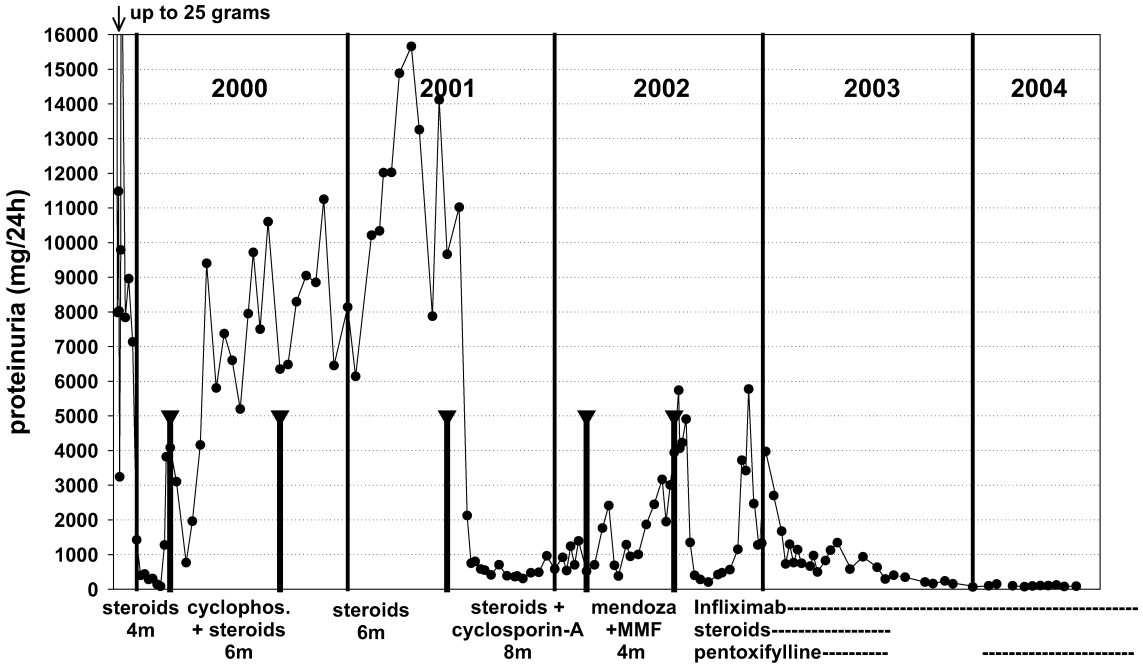

Fig. 1 Nephrotic syndrome: overall course of disease. The years are separated by *full-length vertical lines*; the treatment protocols are separated by *short vertical lines with triangles on top*

not administered. The third treatment protocol (over 5 months) included steroids alone (IV pulses 1 g each, followed by oral prednisone 60 mg/day) accompanied by a mixture of traditional Chinese herbs. There was no response to this protocol. The fourth protocol (over 8 months) included steroids (IV pulses 1 g each followed by oral prednisone 60 mg/day) combined with cyclosporin A at doses giving blood levels of 100–125 ng/ml. After an initial response (lowest proteinuria 311 mg/day), the disease relapsed with proteinuria rising steadily to 1,400 mg/day. The fifth protocol (over 4 months) included steroids, this time as the Mendoza protocol: 14 IV pulses of 1 g methylprednislone each, 6 doses over 2 weeks and the rest over 4 weeks, followed by oral steroids, combined with MMF (CellCept). The proteinuria decreased to 382 mg/day but increased to 1,869 mg/day during the same treatment protocol, and the treatment was considered a failure.

Several alternative approaches were also tried; these included a mixture of traditional Chinese herbs prescribed by a Chinese expert from Cornell Medical Center (N.Y., USA). While the herbs improved the general well being of the patient, this treatment regimen did not affect the proteinuria. Chinese acupuncture and hypnosis also failed.

At this stage, the treating physicians recommended a return to steroids combined with higher levels of cyclosporin A and checking the serum for circulating nephrotic factor/complex [3] (eventually not done). If the nephrotic factor had been found, chronic "protective" plasmapheresis could have been considered after kidney transplantation. During the entire course of 5 years, kidney function tests remained in the normal range.

After failure of treatment five, oral pentoxifylline (oxpentifylline, 400 mg t.i.d.) was started, based on the anti-TNF-α properties of this drug and on the report of a French group from Bezancon in patients with membranous nephropathy [9]. In the face of a significant rise in proteinuria, our 5-month trial of pentoxifylline was also declared a failure. The pentoxifylline was administered following approval of the institution's committee for compassionate protocols.

A monoclonal antibody against TNF-α, Infliximab (Remicade, Shering-Plough, Centocor) [5, 6, 7, 10] was administered IV at an initial dose of 5 mg/kg. The Infliximab was administered following approval of the institution's committee for compassionate protocols. In our patient, unlike in Crohn's disease and rheumatoid arthritis, the time-response relationship was not known because of the complicating heavy proteinuria with possible loss of Infliximab (molecular weight 149,000 daltons) in urine. From an initial proteinuria of 5,000 mg/day, the proteinuria decreased (from 3,946 to 400 mg/day) within 21–24 days, and a second "consolidation" dose was given. As three 1-g IV steroid pulses were given close to the first Infliximab dose, it was not clear whether the good response was due to the IV steroids, to the Infliximab, or to their combination (bearing in mind that the heavy Mendoza protocol failed). The proteinuria relapsed after 2 months (to 3,721 mg/day). A third Infliximab dose resulted in a response identical to the first, within 21–24 days (Figs. 1 and 2). After the fourth dose, the Infliximab was administered every 8 weeks. The first four Infliximab "induction" doses were of 5 mg/kg each (400 mg), the fifth to eighth doses were of 2.5 mg/kg (200 mg) each, and the ninth to eleventh doses were of 1.3 mg/kg (100 mg) each, probably serving as maintenance. The patient has been steroid free for the last 5 months. Current proteinuria is between 67 and 110 mg/day; serum albumin is 4.0 g/l and total cholesterol is 225 mg/dl.

Since the administration of the first dose of Infliximab, routine prospective TNF-α assays have been performed. TNF-α levels were determined using the Immulite assay (DPC, Los Angeles, Calif., USA) as previously reported [11] and are shown in Fig. 2. In view of the consecutive increment in the serum TNF-α levels and the controlled low proteinuria, we assumed that urine leakage of the pentoxifylline would this time be minimal. Therefore it was readministered orally, 400 mg three times per day, with a reduction of the TNF-α levels as shown in Fig. 2.

Discussion

We describe here the successful control of nephrotic syndrome with Infliximab, after failure of all other known protocols to induce remission. We adopted the approach of utilizing anti-TNF-α agents following the literature on its proposed role in nephrotic syndrome [1, 3]. Pentoxy-

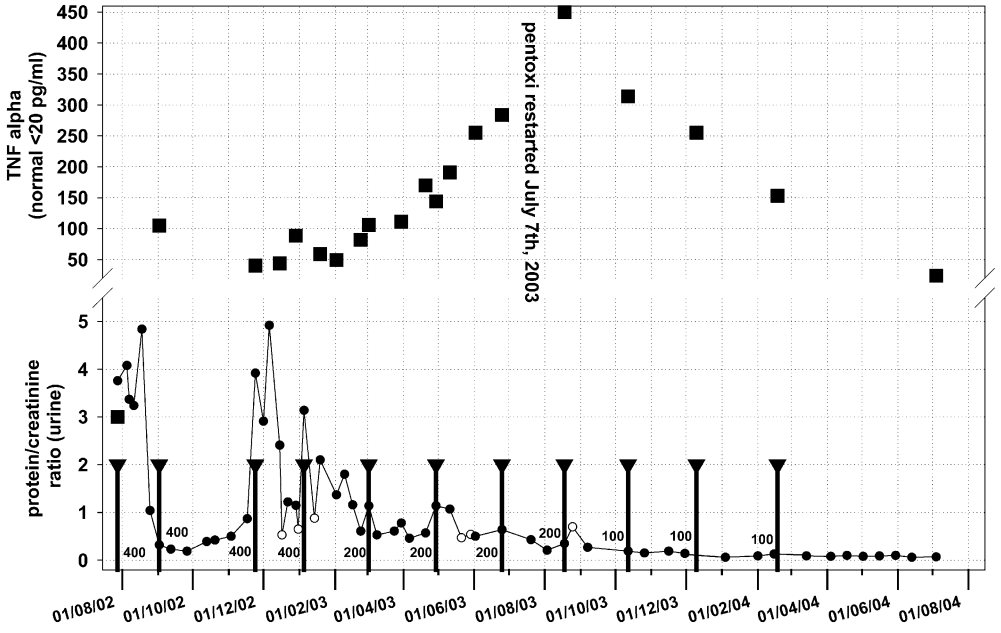

Fig. 2 Response of proteinuria to Infliximab; Infliximab doses next to *short vertical lines with triangles on top*; *TNF-α* in *squares*; ratio calculated from 24-h urine collection

filline was proven in vitro to suppress the production of TNF-α; in addition this effect of pentoxyfilline was reported by the French group in patients with membranous nephropathy. The Infliximab approach was adopted in view of the role of TNF-α in other inflammatory diseases where it is approved for use, as well as its reported effect in congenital nephrotic syndrome [5].

We followed the serum TNF-α levels and found an inverse relationship between the degree of proteinuria and serum TNF-α. We hypothesize that TNF-α is constantly produced at high levels as part of the idiopathic inflammatory process: when proteinuria is high, TNF-α inflicts glomerular damage, but leakage into the urine during periods of high proteinuria considerably reduces its serum levels. When proteinuria is moderate, TNF-α inflicts the same damage, but with less leakage its serum levels are higher. When proteinuria is low and controlled, there is little leakage of TNF-α into the urine, so its serum levels are higher reflecting the intense ongoing inflammatory process. This phenomenon occurred three times, as shown in Fig. 2.

Urinary protein electrophoresis for proteinuria above 1,000 mg/day showed a clear protein band about the size of 20,000 daltons. This band almost disappeared when the proteinuria was below 750 mg/day (TNF-α has a molecular weight of 17,000 daltons). Unfortunately, we could not measure TNF-α levels in the urine.

We suggest that during heavy proteinuria, the TNF-α blocking agents also leak into the urine (the molecular weight of Infliximab is 149,000 daltons). Control of the proteinuria may therefore improve the efficacy of these anti-TNF-α agents. Much smaller molecules with easier leakage into the urine may be wrongly considered not effective at all. This might explain our initial failure with pentoxyfilline (molecular weight 287 daltons, but its protein binding is not clear).

While searching for additional medical approaches, we were aware of anecdotal publications in Chinese as well as in the Western literature about the Chinese herb *Tripterygium wilfordii* Hook F [12, 13, 14]. Unfortunately we could not obtain this herb in a pharmacological preparation. We also were aware of the clinical trial of The Alexion Pharmaceutical Company (Conn., USA) studying the effects of monoclonal antibody directed against the complement component C5 in membranous nephropathy. This clinical trial was open only to membranous nephropathy patients.

In our patient with nephrotic syndrome all standard treatment protocols failed to induce remission. We have successfully controlled the proteinuria with a TNF-α blocking agent and determined the time-response curve of the drug and the proteinuria. Our approach may help similar refractory patients and may diminish the morbidity due to the chronic use of steroids, cyclophosphamide, and cyclosporin A. The use of anti-TNF-α agents might allow control of the proteinuria and hence might prevent renal failure and the need for dialysis and transplantation. Pure human agents (Etanercept, Adalimumab) may minimize the development of antibodies and the need for concurrent immunosuppression. Further controlled studies are warranted to clarify the role of anti-TNF-α agents in idiopathic nephrotic syndrome.

Acknowledgement It is important to note that the first author of this report is the patient's father. The impact that this relationship may have had on treatment decisions for the patient has been carefully considered by all of the authors. The treatment protocol received support from other medical experts, as well as the approval of the local Helsinki committee.

References

1. Suranyl MG, Guasch A, Hall BM, Myers BD (1993) Elevated levels of TNFα in the nephrotic syndrome in humans. Am J Kidney Dis 22:622
2. Bakr A, Shokeir M, El-Chenawi F, El-Husseni F, Abdel-rachman A, El-Ashry R (2003) TNFα production from mononuclear cells in nephrotic syndrome. Pediatr Nephrol 18:516–520
3. McCarthy ET, Sharma R, Scharma M, Li JZ, Ge XL, Dileezpan KN (1998) TNFα increases albumin permeability of isolated rat glomeruli through the generation of superoxide. J Am Soc Nephrol 9:433–438
4. Pai R, Ha H, Kirschenbaum MA, Kamanna VS (1996) Role of tumor necrosis factor alpha on mesangeal cell MCP-1 expression and monocyte migration: mechanisms mediated by signal transduction. J Am Soc Nephrol 7:914–923
5. Drewe E, McDermott EM, Powell RJ (2000) Treatment of the nephrotic syndrome with Etanercept in patients with the tumor necrosis factor receptor-associated periodic syndrome. N Engl J Med 343:1044–1045
6. Verschueren P, Lensen F, Lerut E, Claes K, De Vos R, Van Damme B, Westhovens R (2003) Benefit of anti-TNFα treatment for nephrotic syndrome in a patient with juvenile inflammatory bowel disease associated spondyloarthropathy complicated with amyloidosis and glomerulonephritis. Ann Rheum Dis 62:368–369
7. Pusey C (2001) Efficacy of anti-TNFα in the treatment of nephrotoxic nephritis. Symposium on glomerulonephritis and anti-GBM disease: World Congress of Nephrology (ASN), USA (http://www.hdcn.com/symp/01asn/pu/pusey.htm)
8. Bircan Z, Kara B (2003) Intravenous cyclophosphamide is the drug of choice for steroid dependent nephrotic syndrome. Pediatr Int 45:65–67
9. Ducloux D, Bresson-Vautrin C, Chalopin J (2001) Use of pentoxifylline in membranous nephropathy. Lancet 357:1672–1673
10. Cornillie F, Shealy D, D'Haens G, Geboes K, Van Assche G, Ceuppens J, Wagner C, Schaible T, Plevy SE, Targan SR, Rutgeerts P (2001) Infliximab induces potent anti-inflammatory and local immunomodulatory activity but no systemic immune suppression in patients with Crohn's disease. Aliment Pharmacol Ther 15:463–473
11. Barak V, Nisman B, Polliack A (1999) The tumor necrosis factor family and correlation with disease activity and response to treatment in hairy cell leukemia. Eur J Haematol 62:71–75
12. Li Naisan Yu Dondhui (1992) Study on toxicokinetics of crude extract from *Tripterygium wilfordii*. J Chin Phram Univ 23:25–26
13. Zhang Xiao Chen Shunle (1993) Effect of *Tripterygium wilfordii* Hook F on contrasuppressor T cells in SLE nephritic patients. Chin J Immunol 9:230–231
14. Qiu D, Kao PN (2003) Immunosuppressive and anti-inflammatory mechanisms of Triptolide, the principal active diterpenoid from the Chinese medicinal herb *Tripterygium wilfordii* Hook. F. Drugs 4:1–18