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Immunomodulators: interleukins, interferons, and IV immunoglobulin

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Introduction

The outstanding progress in immunology and the development of new technologies have resulted in the introduction of new immunotherapies, the so-called "immunomodulators", for autoimmune diseases, inflammatory disorders, allograft rejection, and cancer. These immunomodulators comprise recombinant cytokines and specific blocking or depleting antibodies. Many of these therapies achieve their effect by stimulating the release of cytokines. The term cytokines includes interleukins (IL-), chemokines, growth factors, interferons (IFN), colony stimulating factors (CSF), and tumor necrosis factors (TNF). These molecules are involved in inflammation, cell proliferation and apoptosis, tissue injury and repair.

These new therapeutic tools can be associated with side effects among which nephrotoxicity. The most common immunomodulators associated with nephrotoxicity are described in Table 1. The nephrotoxic side effects of immunomodulators can be roughly divided into (ischemic) tubular necrosis, thrombotic microangiopathy, serum sickness, and autoimmune disorders.

This chapter aims to address the nephrotoxic potential of the cytokines or monoclonal antibodies at the doses being used in the treatment of cancer, auto-immune diseases, and transplantation.

Table 1. The most common immunomodulators associated with nephrotoxicity.

Agent	Pharmacological substance	Indications	Renal toxicity	References
Aldesleukine	Recombinant **IL-2**	- Metastatic renal cell carcinoma - Melanoma	- Acute renal failure	9, 15-18
Interferon-α	Recombinant **IFN-α**	- Viral hepatitis - Non-Hodgkin lymphoma - Several other malignancies	- Acute renal failure - Proteinuria - Lupus-like disease - Pauci-immune GN - RPGN - FSGS - Minimal change nephrotic syndrome - Allograft rejection	27, 31, 32, 33-35, 38-40, 42-48, 51, 52, 54, 58, 59
Peginterferon-α	Pegylated **IFN-α**	- Hepatitis C	- Acute renal failure - Exacerbation of vasculitis	60, 61
Interferon-β	Recombinant **IFN-β**	- Multiple sclerosis	- None reported	62, 63
Interferon-γ	**IFN-γ**-1b	- Chronic granulomatous disease	- Proteinuria - Acute renal failure	64, 66, 67
Muromonab (OKT3)	Anti-**CD3** Ab	- Allograft rejection	- Acute renal failure - Thrombotic microangiopathy	76, 78-82
Rituximab	Anti-**CD20** Ab	- Rheumatoid arthritis - Non-Hodgkin lymphoma	- Acute renal failure - Serum sickness	86-89
Infliximab	Anti-**TNFα** Ab	- Rheumatoid arthritis - Crohn's disease - Ankylosing spondylitis	- Serum sickness - Lupus-like disease - Extracapillary glomerulonephritis	90-93
Alemtuzumab (Campath)	Anti-**CD52** Ab	- B-cell chronic lymphocytic leukemia - Preconditioning regimen for bone marrow and renal transplantation	- HUS - Acute renal failure - Acute humoral rejection	98, 99, 101
Intravenous immune globulin (**IVIG**)	Human IgG	- Primary immunodeficiency syndromes - Kawasaki disease	- Acute renal failure	103, 106-108
Thymoglobulin (**ATG**)	Anti-thymocyte globulin	- Acute kidney and liver allograft rejection	- Acute renal failure	110, 111

Pathogenesis

Tubular necrosis

Cytokine associated renal dysfunction is regularly observed in the setting of sepsis syndrome or systemic inflammatory response syndrome. The cytokine release syndrome associated for example with OKT3 administration is similar to systemic inflammatory response syndrome. During systemic inflammatory response syndrome, it has been observed that even in the absence of systemic hypotension, acute tubular necrosis (ATN) can occur. Certain cytokines released during systemic inflammatory response syndrome mediate peripheral vasodilation in the absence of systemic hypotension. The renal response to peripheral vasodilation is vasoconstriction of the renal vasculature and reduced renal blood flow. TNF-α is a pro-inflammatory cytokine which plays a central role in the pathogenesis of systemic inflammatory response syndrome. TNF-α stimulates the secretion of IL-1β and regulates genes coding for other inflammatory mediators such as IL-1, IL-6, IL-8, and macrophage inflammatory protein (MIP-2). The major cellular sources of TNF-α are monocytes and T cells but upon injury, renal tubular cells start also to produce TNF-α as well as other pro-inflammatory cytokines [1-3] leading to an amplification of the inflammatory responses. TNF-α and IL-1 have also been shown to induce glomerular endothelial and mesangial cell production of vasoconstricting mediators like platelet activating factor (PAF), endothelin-1 (ET-1) and adenosine, but also of the vasodilators nitric oxide and prostaglandin E2. Local release of TNF-α reduces glomerular blood flow and glomerular filtration rate, induces the synthesis of other proinflammatory mediators, and, along with reactive oxygen species, increases glomerular albumin permeability. Pro-inflammatory cytokines recruit neutrophils and monocytes to the kidney and enhance their adhesion to endothelial cells.

Thrombotic microangiopathy

Thrombotic microangiopathy results from a massive activation of the clotting cascade. The major initiating factors are the release or expression of tissue factor, usually involving entry of tissue thromboplastins into the circulation, extensive injury to vascular endothelium exposing tissue factor, or enhanced expression of tissue factor by monocytes in response to endotoxin and various cytokines. Very high doses of systemic TNF can cause thrombotic microangiopahy as observed by Bertani in an experimental rabbit model. He showed that an intravenous TNF infusion did induce glomerular endothelial damage, neutrophil accumulation, and fibrin deposition within capillary lumens [4]. TNF-α induces production of reactive oxygen species by mesangial cells and tissue factor production by mesangial and endothelial cells, leading to fibrin deposition [5].

Serum sickness

The originators of the term 'serum sickness' are von Pirquet and Schick, who published a book with that title (Das Serumkrankheit) in 1905 [6]. The authors described an illness that developed in some patients after administration of horse serum that had been given as an antitoxin for the treatment of diphtheria and scarlet fever. Serum sickness is characterized by fever, rash, arthralgias, and eventually glomerulonephritis. Serum sickness is the prototypic example of the Coombs 'type III' or immune complex mediated hypersensitivity disease. The disease requires the presence of the antigen coincident with antibodies directed against the antigen, leading to the formation of antigen-antibody or immune complexes. These should normally be cleared by the mononuclear phagocyte system. If this system is not functioning well or is saturated by the immune complex load, then excess immune complexes may form in the circulation and deposit in tissues, or form directly in the involved tissues. The deposition of antigen-antibody (immune) complexes in tissues triggers the activation of the complement cascade, recruitment of leukocytes, and release of inflammatory mediators, such as histamine. Classic serum sickness can occur after injections of chimeric monoclonal antibodies but a variety of drugs can also cause reactions that clinically resemble classical serum sickness, but are believed to be caused by different mechanisms. In most cases, the specific mechanism is not known.

Auto-immune disorders

Drug-induced lupus is a syndrome which shares symptoms and laboratory characteristics with idiopathic systemic lupus erythematosus (SLE). Similarly

to idiopathic lupus, drug-induced lupus can be divided into systemic, sub-acute cutaneous and chronic cutaneous lupus. The syndrome is characterized by arthralgia, myalgia, pleurisy, rash and fever in association with antinuclear antibodies in the serum. The clinical and laboratory manifestations of drug-induced SLE are similar to those of idiopathic SLE, but central nervous system and renal involvement are rare in drug-induced lupus [7]. Blockade of TNF in human rheumatoid arthritis or Crohn's disease led to the development of autoantibodies, lupus-like syndrome, and glomerulonephritis in some patients. These data raise concern about using TNF-blocking therapies in renal disease because the kidney may be especially vulnerable to the manifestation of autoimmune processes. Interestingly, recent experimental evidence suggests distinct roles for the 2 TNF receptors in mediating local inflammatory injury in the kidney and systemic immune-regulatory functions [8].

Recombinant cytokines

Interleukin-2

IL-2 is a 15 kilodalton glycoprotein which is normally produced by antigen or mitogen activated circulating T lymphocytes. It induces natural killer cell activity, enhances the allogeneic response, and activates cytotoxic T lymphocytes [9].

IL-2 has been used in the treatment of solid tumors such as metastatic melanoma, metastatic renal cell carcinoma, and colorectal carcinoma. Interleukin-2 infusions are associated with significant dose-dependent toxicity characterized by fevers, malaise, nausea, vomiting, diarrhea, hepatic dysfunction, pulmonary edema, somnolence, confusion, dysrhythmias, myocardial infarction, hematopoietic suppression, and renal insufficiency [10]. IL-2 has a short serum half-life of 6-10 min and a clearance of 30-60 min after bolus intravenously infusion [11]. Resultant toxicity is generally transient and reversible. It is possible that IL-2 induced renal failure only occurs in the setting of profound hypotension, prior volume depletion, concurrent administration of potentially nephrotoxic drugs, or the presence of underlying renal disease.

Morroquin *et al*. [12] studied the effect of high-dose IL-2 therapy in the treatment of patients with metastatic melanoma and renal cell cancer. They found that there was a subset of patients who could not tolerate high doses or retreatment due to renal toxicity. Pre-treatment factors that were significantly associated with renal toxicity were male sex, diagnosis of renal cancer, previous nephrectomy, and older age. These patients also had higher baseline creatinine.

Kozeny [13] evaluated IL-2 associated fluid and electrolyte disorders in 8 patients with metastatic cancer. All patients developed capillary leak syndrome, pre-renal azotemia, hypophosphatemia, hypocalcemia, hypomagnesemia, and respiratory alkalosis. As noted in other studies, albumin fell precipitously with an associated fall in serum calcium. However, measurement of ionized calcium and urinary calcium demonstrated true hypocalcemia and hypocalciuria. There was an associated hypomagnesemia and hypomagnesurea, hypophosphatemia, hypophosphaturea. Primary hyperventilation and respiratory alkalosis were thought to have caused an increased binding to albumin and intracellular shifts of these ions. Likewise, severe hypophosphatemia can be seen in gram negative sepsis in association with respiratory alkalosis. All patients developed a compensatory metabolic acidosis due to chronic hyperventilation. Respiratory alkalosis was thought to have developed because of capillary leak into the lungs producing borderline or frank pulmonary edema. After several days a superimposed normal anion gap acidosis developed from dilution by large volumes of saline fluid resuscitation. The authors found no defects in renal handling of calcium, phosphorous, or magnesium. There was no evidence of a renal acidification defect or renal tubular acidosis.

Shalmi *et al.* [14] suggested that an intrinsic renal defect may contribute to the renal dysfunction since the creatinine appeared to increase out of proportion to the blood urea nitrogen. If the predominant lesions were pre-renal azotemia, one would expect relative preservation of glomerular filtration rate in the face of renal hypoperfusion, thereby increasing the filtration fraction. The urinalysis did not show an active sediment as one might see in acute tubular necrosis. The authors suggested that the generalized capillary leak syndrome associated with the administration of IL-2 might have contributed to intra-renal edema and congestion leading to increased back-pressure and a decrease in ultrafiltration pressure and glomerular filtration rate.

Vlasveld [15] obtained biopsy material from a pa-

tient with renal cell cancer who developed acute renal failure in the sixth week of a continuous rIL-2 infusion. Acute tubulo-interstitial nephritis was present on pathology. Further studies on cryopreserved peripheral blood lymphocytes revealed specific cytotoxic activity against an autologous renal cell line cultured from the biopsy specimen.

In the past indomethacin was commonly given as prophylaxis against the chills, fever, arthralgias, myalgia's, and malaise associated with IL-2 administration. Non-steroidal anti-inflammatory drugs (NSAIDs) block prostaglandin-mediated glomerular afferent arteriolar vasodilation that is part of the auto-regulatory response to hypotension and renal hypo-perfusion. Co-administration of an NSAID with IL-2 sometimes precipitated acute renal failure.

Belldegrun [9] studied 99 patients with various types of metastatic cancer who had no identified renal disease, had a serum creatinine <1.9 mg/dl (despite unilateral nephrectomy in some) and had no autoimmune disorders and no exposure to immunosuppressive drugs. A confounding factor in the study was the prophylactic administration of indomethacin. The mean percentage of increase in creatinine was 219±15%. Mean peak serum creatinine level correlated with dose of IL-2 administered. Patients with baseline elevation of serum creatinine greater than 1.4mg/dl, renal cell carcinoma and radical nephrectomy represented a high risk group who were more sensitive to the IL-2 regimen and had a prolonged recovery of renal function. Weight gain and edema were observed in conjugation with the renal dysfunction. Textor *et al.* [16] noted progressive hypotension, sodium avidity, weight gain and edema, diminished glomerular filtration rate and evidence of ongoing tubular injury after administration of recombinant interleukin-2 to 12 patients. All patients received indomethacin which may have contributed to the development of acute renal failure. Serum creatinine returned to normal one week following discontinuation of therapy. The above 2 studies were seriously flawed because of the co-administration of NSAIDs.

Administration of cytokine combinations may be synergistic in their toxicity. Dutcher *et al.* reported a phase II trial of outpatient subcutaneous IL-2 plus IFNα [17]. They noted higher grade toxicity of fatigue, nausea, vomiting diarrhea, anorexia, fluid overload, rash, aseptic meningitis, chest pain, atrial fibrillation, and hypotension. One patient developed irreversible, dialysis dependent renal failure with crescentic glomerulonephritis.

Negrier *et al*. have compared the toxic effects of IL-2 and IFN-α in a cohort of 425 patients with metastatic renal cell carcinoma [18]. They found that the response rate of IL-2 and IFN-α were comparable, whereas the response rate of combined IL-2 and IFN-α therapy was significantly higher than during monotherapy. Nephrotoxicity however, was more common in patients receiving IL-2 than in those receiving IFN-α. Interestingly, Schomburg [19] demonstrated that palliative low to intermediate-dose of IL-2 in combination with IFN-α therapy was less nephrotoxic and less vasculo-toxic, especially if given subcutaneously rather than intravenously. Although there was a significant increase in serum creatinine and blood urea nitrogen (mean peak of 115.1±21.4 mmol/l, 6.5±2.5 mmol/l), there was no clinical evidence of renal dysfunction.

IL-2 appears to cause a generalized increase in capillary permeability, reduced systemic vascular resistance, fluid shifts and low effective circulating blood volume. It is not known if the vascular effects are a direct effect of IL-2 or due to IL-2 induced release of other mediators such as IFN, IL-1, TNF, and lymphotoxin [11, 20].

Rosentein *et al.* [21] injected high dose IL-2 into mice followed by intravenous I^{125} bovine serum albumin as a marker of capillary leak. The severity of the vascular leak syndrome was dependent upon the number of days of treatment and the dose given. Severity could be reduced by immune suppression with cyclophosphamide, corticosteriods, or whole body irradiation implying that lymphokines released by lymphocytes placed a role in the induction of the vascular leak phenomenon.

Renal toxicity has been attributed to sequelae from the development of the capillary leak syndrome. Vascular leak resulted in significant extravascular fluid accumulation (ascites, pleural effusions, peripheral edema) and weight gains of as much as 17 kg in 3 weeks [11]. As in sepsis syndrome, hypotension, oliguria and reduced fractional excretion of sodium accompanied the capillary leak.

Ponce treated 5 patients who had metastatic colorectal carcinoma with continuous intravenous infusions of IL-2 for 5 days and 9 cycles. They attempted to maintain a stable blood pressure with aggressive fluid replacement. However systemic vascular resistance declined from 1304 to 871 dyn/s/cm-5 and mean

arterial blood pressure still dropped from 105 to 86 mm/Hg. Urine output dropped significantly and serum creatinine rose significantly. Urine sediment was normal on day 1 but contained multiple epithelial cells and brown casts by day 5 [22].

Others have shown that oliguria accompanying IL-2 infusions, responds to low-dose dopamine infusions, fluid resuscitation, and alpha agonists such as phenylephrine [20, 23, 24].

Rafi-Janajreh et al [25] examined the mechanism of IL-2 induced vascular leak syndrome in a mouse model. The vascular leak was especially significant in the lung and liver of wild-type mice but was markedly reduced in the lungs and liver of CD44 knockout mice. Both groups had similar levels of perivascular infiltration with lymphocytes but the CD44 knockout mice did not have endothelial cell damage and also exhibited a marked decrease in IL-2-induced lymphokine-activated killer cell activity. These investigators also showed that the vascular leak syndrome was dependent on the expression of CD44 on immune cells and not on the endothelial cells.

The above-mentioned studies have suggested or proposed a direct renal injury by IL-2, but none of them have been able to conclusively distinguish a direct IL-2 renal effect from simple renal under-perfusion severe enough to cause ischemia and ATN. The toxicity of IL-2 has been clearly associated with widespread endothelial cell damage and capillary leak [25]. This is consistent with a generalized, systemic effect of IL-2 rather than proof of a specific direct effect on the kidney.

Hall *et al*. [26] examined the nephrotoxic effects of IL-2 and its putative mediator, TNFα, in a pig kidney cell line. Levels of IL-2 comparable to those used in human studies, caused vacuolization, cell shrinkage and growth inhibition. Dexamethasone, which is used clinically to inhibit TNFα, failed to protect the cultured cells from the effects of IL-2. TNFα when given alone had no apparent effect on morphology or cell growth, suggesting that the nephrotoxic effect of IL-2 was direct.

Interferons

IFNα and IFNβ share 29% amino acid homology. Type I IFN (α and β) differ from Type II IFN (γ) in biochemical properties, biological function, and receptor specificity. Side effects common to both classes of IFN include chills, fever, rigors, headache, myalgia's, hypotension, nausea, vomiting, anorexia, constipation, fatigue, neutropenia, and elevated transaminases. This constellation of symptoms frequently results in mild to moderate hypotension and volume depletion and could potentially contribute to pre-renal azotemia or ATN.

Interferon-α

IFNα has anti-viral and anti-proliferative effects which have proven useful in the treatment of hepatitis B and C, cryoglobulinemia, and various tumors including rectal cancer, lymphoma, breast cancer, ovarian malignancies, cutaneous T-cell leukemia (mycosis fungoides), bladder cancer, cervical dysplasia, melanoma, and chronic lymphocytic lymphoma. Side effects include fever, chills, malaise, headache, myalgia's, neuropathy, somnolence, confusion, and fatigue. Leukopenia and elevation of serum transaminases are the most common dose limiting side effects. Nephrotoxicity is uncommon and usually noted in individual case reports as an association with administration of IFNα. Often there are other factors contributing to acute renal failure such as concomitant renal disease (nephrectomy, hepatitis C infection, or nephrotoxic drugs). Phillips reviewed this topic in 1996 [27]. Gutterman [28] reported no effects of treatment on serum creatinine and blood urea nitrogen, although transient pyuria was noted in 5 of 16 patients. Abdullhay [29] noted mild elevations of blood urea nitrogen and creatinine in 10 patients and more severe dysfunction in 2 of 36 patients with ovarian malignancies. The latter 2 patients had prior renal impairment.

Reports of isolated proteinuria associated with IFNα therapy have cropped up in the literature. Sherwin [30] observed 2 patients with transient proteinuria of less than 2 g/day which recurred with rechallenge with IFNα. Quesada [31] initially reported proteinuria of less than 2 g/day which recurred with rechallenge with IFNα. In a later publication, Quesada [32] cited an overall incidence of non-dose related proteinuria in 15-20% of patients. Quantitation rarely exceeded 1 gram and was not associated with a decline in glomerular filtration rate. Ferri [33] also noted proteinuria in patients being treated for mixed cryoglobulinemia but admitted that subclinical glomerular involvement with cryoglobulins could have been present. A few cases of

acute renal failure and nephrotic syndrome have also been reported [34, 35].

As far back as 1976 IFNα was shown to be able to induce glomerulonephritis in animal models. Gresser [36] was able to develop an animal model of acute glomerulonephritis (GN) by injecting high dose IFNα into mice. Experimental evidence supports an immunologic effect of IFNα the kidney. Morel-Maroger [37] injected partially purified mouse interferon into newborn mice and found marked thickening of the glomerular basement membrane preceding the deposition of immunoglobin and complement.

Since then there have been a number of case reports of IFNα associated GN in humans. A variety of lesions have been reported including minimal change disease, pauci-immune GN, rapidly progressive GN, and focal segmental glomerulosclerosis [38, 39]. Two studies reported the onset of a nephrotic syndrome during treatment with IFNα. The nephrotic syndrome reversed after treatment was withdrawn [34, 40]. Herman [41] published a report of a patient with hairy cell leukemia who developed mesangio-capillary GN during treatment with IFNα. He developed hematuria, pyuria, and depressed complements. Colovic reported a patient with Philadelphia chromosome positive CML and nephrotic syndrome in whom renal insufficiency developed after the onset of IFNα treatment [42]. A renal biopsy showed the characteristics of mesangiocapillary glomerulonephritis. In spite of the discontinuation of treatment, renal function deteriorated and the patient died six months after the onset of the symptoms. Averbuch [43] reported a patient with Mycosis Fungoides who developed a minimal change nephropathy and acute interstitial nephritis after 6 doses of IFNα. After IFNα was discontinued, renal function returned to normal, but low grade proteinuria persisted for 2 months. Rechallenge with IFNα again produced azotemia and nephrotic range proteinuria. The authors suggested that activated cytotoxic T cells were responsible for a cell mediated delayed hypersensitivity mechanism of injury. Similar cases of minimal change disease associated with IFNα were reported by Traynor et al [44] and Rettmar et al [45]. Shah et al reported 2 cases of renal failure associated with IFNα treatment of chronic myeloid leukemia. Both patients had proteinuria and focal segmental glomerulosclerosis on biopsy [46]. Recently, two case reports were issued that concerned the occurrence of acute renal failure in patients that were treated with IFNα for metastatic carcinoid tumors [47, 48]. In both cases, renal function recovered after cessation of therapy.

Unusual immune side-effects have also been reported in association with IFNα therapy. Chronic hemolytic uremic syndrome was observed in a patient with multiple myeloma treated with IFNα (De Broe ME, personal communication). The post bone marrow transplantation course was complicated and he received several nephrotoxic antibiotics. Three months later a treatment with IFNα was started. Towards the end of the treatment renal function deteriorated. There was partial renal recovery after cessation of therapy. Renal biopsy showed focal mesangio-capillary lesions, mesangiolysis and intracapillary thrombosis consistent with a chronic form of hemolytic uremic syndrome. Ravandi-Kashani et al. [49] and Harvey et al. [50] reported 3 other cases of HUS/TTP. Two patients developed renal failure requiring dialysis. E. coli OH157.H7 was grown from the stool of one patient.

Acute renal failure or deterioration has frequently been cited in association with IFNα treatment of hepatitis C and even hepatitis B. It is well known that hepatitis C virus infection can cause GN. Mesangiocapillary GN is the most common manifestation and biopsy specimens have shown deposition of immune complexes composed of hepatitis C virus-related antigen and cryoglobulin. The difficulty lies in distinguishing glomerulonephritis caused by hepatitis C from glomerulonephritis seen in association with IFNα therapy or from occult underlying renal disease that is exacerbated by IFNα. There have been reports of nephrotic range proteinuria and focal segmental glomerulosclerosis on biopsy in patients who are being treated with IFNα for hepatitis C [51, 52]. Gordon *et al.* [53] reported a case of IFNα induced exacerbation of vasculitis (rash and renal impairment) in a patient with hepatitis C-associated cryoglobinulemia. Ohta *et al.* [54] examined 24 patients who manifested the appearance of or exacerbation of proteinuria after IFN therapy for chronic hepatitis C infection. One patient had known hepatitis C-related glomerulopathy and cryoglobulinemia and showed a good response to therapy including improved renal function and remission of proteinuria. Yamabe *et al.* and also Sarac *et al*. confirmed good responses to IFN therapy without renal deterioration in patients with hepatitis C-related glomerulonephritis [55, 56]. In Ohta's study only 3 subjects were treated

with IFNα, the remainder were treated with IFNβ. As was shown by Johnson [57] improvement in mesangiocapilarry GN with IFNα correlated with clearance of viremia but did not correlate with remission of proteinuria. Other results were quite variable. The authors felt that absence (or minimal presence) of Hepatitis C core antigens or cryoglobulin deposits in the glomeruli indicated non-hepatitis C virus related or primary GN and that these patients might be at higher risk for exacerbation or direct injury from IFN. There was no clear explanation for which patients would benefit from or fail to respond to IFN and which patients might develop irreversible renal injury.

Renal transplant patients with hepatitis C seem to be especially susceptible to injury from IFNα. IFNα triggers renal graft rejection in a substantial number of patients, and is now considered contra-indicated in this setting [58, 59].

In recent years, pegylated IFN (peginterferon) in combination with ribavirin has shown to attain higher virological response rates in chronic hepatitis C than standard interferon. Therefore, Peginterferon-α is rapidly becoming the standard of care for chronic hepatitis C infections. Peginterferon is produced by the addition of a polyethylene glycol molecule to standard interferon alfa-2 and results in important changes in drug metabolism, with marked prolongation of its half-life. Peginterferon-α causes virtually no toxic side effects and hitherto only two case reports on renal adverse effects of this medicine have been published. Gordon described the case of a 54-year-old patient, who developed acute renal failure nine days after commencing treatment [60]. A renal biopsy showed ATN, and exacerbation of (probably pre-existent) IgA-nephropathy. After cessation of therapy, renal function was restored. In addition, Batisse described exacerbation of cryoglobulinemia-related vasculitis in one patient, following treatment of hepatitis C with peginterferon-α [61]. Symptoms included a purpuric rash, peripheral neuropathy and acute renal failure, which resolved slowly after discontinuation of peginterferon-α therapy.

In summary, other symptoms of IFNα toxicity are far more common than nephrotoxicity (fevers, chills, malaise, arthralgias, fatigue anorexia, weight loss, depression, impaired cognitive function, diminished libido, abnormal thyroid function). Nevertheless, IFNα has a complicated and important relationship to the kidney but there are many confounding factors that tend to obscure the molecular dynamics of that relationship.

Interferon-β

IFNβ has been used in the treatment of multiple sclerosis. IFNβ has been also used in combination with IFNγ because of synergistic anti-tumor effects. The combinations of IFN appear to potentiate systemic effects and cumulative toxicity compared to administration of either interferon alone. Synergistic toxicity limits the tolerated dose maximum and may also limit efficacy. Low doses of IFN-β and -γ given in combination, either by intravenous bolus or continuous infusion, do not appear to cause renal damage or dysfunction [62, 63].

The particular renal effects of IFN-β have not been specifically evaluated. Increased insensible losses via skin or the gastrointestinal tract or fluid sequestration from capillary leak and hypoalbuminemia can contribute to the development of pre-renal azotemia. Volume depletion and hypotension stimulate Angiotensin II and renal sympathetic nerves to try to maintain filtration fraction. Angiotensin II is a potent vasoconstrictor and also up-regulates the expression of growth factors and cytokines such as TGFβ, TNFα, vascular cell adhesion molecule-1 (VCAM-1), platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF) and insulin-like growth factor that are involved in renal injury and repair.

Interferon-γ

There are several subspecies of IFNγ determined by differential glycosylation. IFNγ is the most potent immunomodulator of all IFN. IFNγ is cidal to human tumor cell lines, activates monocyte/macrophages, upregulates Class II MHC expression and increases natural killer cell activity [64]. In the kidney, IFNγ regulates Class I and II MHC expression in the basal state, in response to inflammatory stimuli, and after ischemia or ischemia-reperfusion renal injury [65].

Systemic side effects are similar to those of other IFN, namely fever, chills, rigors, hypotension, confusion, disorientation, anorexia, lethargy, nausea, vomiting, diarrhea, myalgia, leukopenia, hepatotoxicity. Side effects are reversible and limited to the time of administration of the drug. Mild changes in liver

function have been observed at higher dose levels and include hypoalbuminemia. There have been no significant changes noted in blood urea nitrogen and creatinine, although a small degree of proteinuria has occasionally been observed [64, 66].

Ault [67] reported a case of acute renal failure in a 12 year old child which required temporary hemodialysis after 19 days of therapy with IFNγ. The urinary sediment contained numerous white cells, red cells, and waxy and granular casts. Open renal biopsy revealed focal segmental glomerosclerosis in 3 of 43 glomeruli and irregular wrinkling of the capillary walls in others. A tuft adhesion to Bowman's capsule was seen in one glomerulus. There was also diffuse tubular damage and interstitial edema consistent with acute tubular necrosis. Electron microscopy demonstrated foot process effacement. Direct immunofluoroscence was negative for IgG, IgA, IgM, kappa and lambda light chains, C3, Clq, properdin, and fibrin reactive products. Renal function returned to normal after withdrawal of the drug. The authors suggested that structural distortion of the basement membrane and absence of immune complexes was evidence for direct glomerular injury by the cytokine. However the authors could not exclude prior sub-clinical focal and segmental glomerulosclerosis in the child. To support their hypothesis, the authors cited studies in newborn Swiss mice exposed to mouse interferon in which there was diffuse glomerular basement membrane wrinkling and capillary IgG and C3 deposition which progressed to focal segmental glomerulosclerosis.

Monoclonal antibodies

Monoclonal antibodies can vary tremendously in terms of isotype, construction (animal derived, chimeric, humanized, bound to toxin), ability to activate complement, binding avidity, target specificity, and whether it binds and blocks or binds and activates the receptor. Monoclonal antibodies may be directed toward soluble or membrane bound receptors or receptor ligands, tumor antigens, growth factor or their receptors. Therefore toxicity and side effects are equally variable [68].

In general, complement-binding monoclonal antibodies are more likely to cause a first dose response and cytokine release and potentially renal failure.

Monoclonal antibodies that are associated with systemic response consistent with cytokine release include:

Anti-CD3 antibodies

OKT3 is a murine monoclonal antibody recognizing the CD3 complex closely associated with the T cell receptor (TCR). The immunosuppressive properties of OKT3 are related to its ability to deplete CD3+ T cells, to induce the internalization of the CD3-TCR complexes, and to sterically inhibit residual CD3-TCR complexes [69]. The ability of OKT3 to induce multivalent cross-linking of both the TCR-CD3 complexes and the monocyte Fc receptor results in T cell and monocyte activation [70]. This is accompanied by the systemic release of pro-inflammatory cytokines including TNF-α, IFN-γ, IL-2 and IL-6 [71-75]. This leads to a cytokine release syndrome similar to systemic inflammatory response syndrome. This is associated with the development of a transient renal dysfunction [76]. In some cases renal biopsies were obtained at the time of renal dysfunction that showed only mild interstitial edema [77]. Beside the transient kidney dysfunction described above, OKT3 exerts pro-coagulant effects which can precipitate intragraft thromboses [78-82].

Anti-CD4

Anti-CD4 monoclonal antibodies have been used in the treatment of rheumatoid arthritis, psoriasis, systemic lupus erythematosus, and multiple sclerosis. First dose reactions were observed consisting of dyspnea, chills and hypotension [83].

Anti-CD20 antibodies

Rituximab, a B cell-depleting chimeric anti-CD20 monoclonal antibody, has been used with increasing frequency in the treatment of rheumatologic diseases. First dose effect was noted with rituximab (fever, rigors, hypotension) suggesting cytokine release. Some patients have experienced severe hypotension with the first two infusions [84, 85]. Recent publications reported the occurrence of serum sickness in patients with autoimmune diseases and marked hypergammaglobulinemia [86]. Also in patients suffering from hematological malignancies such as mantle cell lymphoma [87] and marginal zone B-cell lymphoma [88]

rituximab-induced serum sickness has been described. Usually, there are no, or only mild renal side effects. Recently however, Ramamoorthy presented an unusual case of a 56-year-old man, who developed intravascular hemolysis, rhabdomyolysis and acute renal failure upon treatment with rituximab for high-grade non-Hodgkin lymphoma [89].

Anti-TNF antibodies

Despite a good overall safety profile, anti-TNF antibodies can induce a number of adverse effects, including autoimmunity and infections. A trial in the treatment of Crohn's disease noted infusion reactions, transient increased of anti-dsDNA antibodies, and serum sickness-like delayed hypersensitivity with re-treatment. Induction of human-antichimeric-antibodies was suggested as the cause of some of the infusion reactions [90]. A prospective study in 35 patients with Crohn's disease showed induction of ANA and anti-dsDNA autoantibodies in 53% and 35% of infliximab-treated patients [91]. A single patient showed clinical features consistent with drug-induced lupus, including the presence of ANA and anti-dsDNA autoantibodies, which quickly resolved after discontinuation of infliximab. Reports on renal adverse effects of anti-TNF antibodies are very rare. Saint Marcoux described the occurrence of crescentic GN in as few as 2 patients out of a cohort of 39 patients, treated with an anti-TNF antibody for rheumatoid arthritis [92]. A case report by Chin *et al*. [93] described the case of a 29-year-old Australia-born Vietnamese who presented with nephrotic syndrome. A renal biopsy showed membranous nephropathy. Symptoms attenuated after discontinuation of infliximab therapy.

Etanercept is a recombinant dimeric fusion protein consisting of a TNF-α receptor ligand-binding region linked to the Fc portion of human IgG, used in the treatment of rheumatoid arthritis, ankylosing spondylitis, juvenile rheumatoid arthritis and psoriasis. Since 1998, there have been reports of vasculitic adverse events, including necrotizing vasculitis and leukocytoclastic vasculitis [92]. Etanercept has relatively little renal toxicity [94]. Recently, a case report was published that described the occurrence of Henoch-Schönlein Purpura, 11 months after starting etanercept therapy for psoriasis in a 57-yr old man [95]. Purpura was accompanied by renal failure, proteinuria and hematuria with red blood cell casts. Symptoms disappeared after discontinuation of etanercept. A second case study by Stokes described onset of renal failure, 4 months after initiation of etanercept therapy for rheumatoid arthritis [96]. On renal biopsy, the diagnosis of pauci-immune crescentic GN was established.

Anti-IL-2 Receptor

Of note, the *anti-IL-2 Receptor* (alpha chain) antibodies daclizumab and basiliximab, widely studied in renal transplant recipients, did not induce cytokine release or first dose reactions [97].

Anti-CD52-antibody

Campath-1H is a humanized CD52-specific depleting complement-fixing cytotoxic IgG1 monoclonal antibody. CD52 antigen is located on the surface of T and B lymphocytes, natural killer (NK) cells, and less densely on monocytes. Campath-1H depletes T lymphocytes from the peripheral blood for several months. Anti-CD52-Ab is used in the treatment of chronic lymphocytic leukemia, as induction therapy in renal transplantation and as a conditioning agent for bone marrow transplantation. Recently, a limited number of studies have been published that demonstrate possible renal adverse effects of anti-CD52-Ab. Bonatti reported the occurrence of hemolytic uremic syndrome in a renal transplant patient treated with Campath-1H [98]. In addition, Osborne described the case of a 37 year old woman who developed acute renal failure and disseminated intravascular coagulation following one dose of Campath-1H and Fludarabine, in preparation for bone marrow transplantation [99]. Campath-1H was thought to be the most likely causal agent although Fludarabine alone or in combination with Campath cannot be excluded. Renal function did not recover, requiring dialysis treatment up to 9 months after onset of symptoms. Recently, in a retrospective study in 443 renal transplant patients with biopsy-proven glomerular disease, the recurrence of glomerular disease under treatment with Campath-1H was studied [100]. In this study, the recurrence of biopsy-proven glomerular disease was similar in patients induced with Campath-1H or IL-2 receptor antagonists, while patients receiving antithymocyte antibody had a borderline lower recurrence rate than patients treated

with other induction agents (P=0.047). Hill presented the rare case of a 38-yr-old renal transplant patient, who developed severe early acute humoral rejection, resulting in allograft loss after Campath-1H induction therapy [101].

Intravenous immune globulin

Intravenous immune globulin (IVIG) is purified, sterile IgG derived from pooled human plasma. Stabilizing agents such as glucose, maltose or sucrose are added in high concentrations in order to prevent or reduce immunoglobulin aggregation. IVIG modulates cytokine production and down-regulates IL-1, IL-2, IL-3, IL-4, IL-5, IL-10, TNFα, and granulocyte-macrophage colony-stimulating factor (GM-CSF). However, flushing, myalgia, headache, fever, chills, wheezing, hypotension and tachycardia have been noted after the start of the infusion and have been attributed to activation of complement and the complement cascade. Reversible rises in serum creatinine occurred in 4/17 patients treated for ANCA-associated vasculitis [102].

Acute renal failure is a well-recognized but infrequent finding after IVIG treatment and is thought to be at least partly related to the high solute load-induced injury to the proximal tubule [103]. Indeed, renal biopsies from patients with IVIG-induced acute renal failure show swelling and vacuolization of proximal tubular epithelial cells, leading to obstruction of the tubular lumen [104]. Other studies have shown that intravenous immunoglobulin infusions are more likely to result in acute renal failure in the presence of underlying renal disease or with simultaneous use of certain other drugs such as non-steroidals and angiotensin-converting-enzyme inhibitors.

IVIG is increasingly used in the treatment of auto-immune nephropathies, mainly lupus-nephritis and ANCA-associated glomerulonephritis [105]. In these diseases, IVIG is reported to reduce proteinuria and improve renal function (comprehensively reviewed by Orbach *et al.* [105]). However, the occurrence rate of acute renal failure in patients with lupus-nephritis and ANCA-associated glomerulonephritis, treated with IVIG), seems higher than in patients with other auto-immune diseases, although prospective studies are still lacking. Generally, the injury is reversible [106, 107]. More severe acute renal failure was noted in a patient who had underlying mixed cryoglobulinemia [108].

Although acute renal failure is an infrequent complication of IVIG therapy, clinicians should monitor renal function and sucrose-containing products should be avoided, especially in older patients with preexisting renal disease, dysfunction of other organs or volume depletion.

Anti-thymocyte globulin

Anti-thymocyte globulin (ATG, thymoglobulin) is a polyclonal rabbit antithymocyte globulin that has been used as an immunosuppressive agent in kidney and liver transplant patients. Despite a fairly high safety profile, reported side effects of ATG include hypertension, leucopenia and ARDS [109]. Renal adverse effects are extremely rare; only two case reports describe the occurrence of acute renal failure in patients treated with ATG [110, 111]. Cessation of ATG therapy in both cases and plasmapheresis in one case resulted in full recovery.

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