Use of Cytotoxic Agents and Cyclosporine in the Treatment of Autoimmune Disease

Part 1: Rheumatologic and Renal Diseases

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When cytotoxic agents were initially introduced, their ability to disrupt nucleic acid and protein synthesis led to their effective use for the treatment of neoplastic disease. During the course of this use, however, it became apparent that these agents also suppress the immune system. This usually unwelcome effect was subsequently studied and beneficially directed toward the treatment of non-neoplastic diseases in which autoimmune mechanisms were considered important to pathogenesis. As a result of these investigations, cytotoxic agents and, more recently, cyclosporine have emerged to become an important part of the therapeutic regimen for many autoimmune diseases. Nonetheless, these medications may still cause treatment-induced illness or even death. It is therefore particularly important to weigh the benefits and risks of cytotoxic therapy when treating a non-neoplastic disease.

This two-part Clinical Staff Conference reviews data on the efficacy and toxicity of cytotoxic drugs and cyclosporine in selected autoimmune diseases. Part 1 examines the manner in which these agents have been used to treat rheumatologic and renal diseases.


Dr. Carol A. Langford (National Institute of Allergy and Infectious Diseases, National Institutes of Health [NIH], Bethesda, Maryland): Twenty-five years ago, an NIH conference reviewed an emerging body of literature in which cytotoxic agents were being applied to the treatment of non-neoplastic diseases (1). In the earliest stages of study, it was thought that these novel therapies might supersede glucocorticoids in the treatment of autoimmune disease. What has emerged instead is a much more disease-specific role in which the relation of cytotoxic agents to glucocorticoids is often unique and at times complementary. In some instances, cytotoxic agents are used alone or with glucocorticoids from the outset; in others, they are added later for particular therapeutic efficacy or for glucocorticoid-sparing.

The main cytotoxic agents that have been studied in autoimmune disease include cyclophosphamide, methotrexate, azathioprine, 6-mercaptopurine, and chlorambucil. Although the ability of these drugs to destroy cells led to their initial use for the treatment of neoplastic disease, it became apparent that these drugs also suppress the immune system. The actual mechanism of action has not been clearly established, but immunosuppression is hypothesized to be responsible for the effectiveness of these agents in autoimmune diseases. Unfortunately, their effect on the immune response is not limited to pathways that may play a role in disease. Both cellular and humoral host defense are broadly suppressed, an effect that specifically interferes with the response to infection and immune surveillance. As our understanding of the immune response has grown, the hope has been to therapeutically target the factors thought to be responsible for disease while leaving protective host mechanisms intact.

One of the first such agents to be developed is cyclosporine, a T-cell-selective immunosuppressive drug. Although cyclosporine is not cytotoxic, its inclusion in this review is appropriate because it is increasingly used in autoimmune disease and provides a link to the selective immunosuppressive therapies that are likely to gain importance in the next 25 years.

Cytotoxic agents and cyclosporine have, in many instances, become an established part of therapy for autoimmune disease, but it is important to understand the data supporting their use so that treatment planning is optimized and the substantial side effects of these agents are known. Although much of the initial data on toxicity was accumulated in the setting of cancer treatment, these agents can cause illness or death even at the doses used to treat autoimmune disease. For this reason, the risks of treatment with a cytotoxic agent or cyclosporine must always be weighed against the potential benefits.
This two-part Clinical Staff Conference examines the current understanding of the efficacy and toxicity of cytotoxic drugs and cyclosporine in selected autoimmune diseases. In part 1, we examine how these agents have been used to treat rheumatologic and renal diseases. In part 2, to be published in the 1 July 1998 issue, we discuss their role in inflammatory bowel disease and systemic vasculitis and review therapeutic toxicity, emphasizing the strategies that can be used to monitor for and minimize drug-related side effects.

Rheumatologic Diseases

Dr. John H. Klippel (National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH): Cytotoxic drugs are an important class of agents for the treatment of systemic inflammatory rheumatic disorders. The clinical syndromes for which these drugs are used show marked clinical heterogeneity but share the presence of circulating autoantibodies, local vascular abnormalities, and immune-cell infiltration or antibody deposition at sites of organ abnormality. The factors that ultimately determine tissue destruction in these diseases are poorly understood but presumably involve cumulative pathologic insults produced by immune cells and their mediators.

Table 1. Status of Cytotoxic Drugs and Cyclosporine in the Major Systemic Rheumatic Diseases

<table>
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<tr>
<th>Condition</th>
<th>Approach to Therapy</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Weekly methotrexate on background of nonsteroidal anti-inflammatory drugs or low-dose glucocorticoids has become standard therapy; recent evidence suggests the important role of combinations of immunosuppressive agents (such as methotrexate–cyclosporine), particularly early in disease course; daily cyclophosphamide is effective but should be reserved for patients with vasculitis or severe, treatment-resistant arthritis</td>
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<tr>
<td>Systemic lupus erythematosus</td>
<td>Intravenous cyclophosphamide is clearly effective in relapsing and (probably) other major organ involvement (such as central nervous system disorders, cardiopulmonary conditions, and vasculitis); azathioprine and methotrexate are beneficial in arthritis, serositis, and skin disease that is unresponsive to glucocorticoids or as glucocorticoid-sparing drugs</td>
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<tr>
<td>Inflammatory myopathies</td>
<td>Weekly methotrexate or azathioprine combined with high-dose glucocorticoids have become standards of early drug treatment of polymyositis or dermatomyositis; preliminary evidence suggests efficacy of combinations of agents (such as methotrexate–azathioprine and methotrexate–cyclosporine); intravenous cyclophosphamide has little effect on myositis but is probably beneficial in progressive interstitial pneumonitis</td>
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<tr>
<td>Scleroderma</td>
<td>Role in skin disease is unclear; some evidence suggests that methotrexate or cyclosporine may be beneficial; intravenous cyclophosphamide is effective in progressive interstitial pneumonitis</td>
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cyclophosphamide is infrequently used because of concern about toxicity except in patients with systemic rheumatoid vasculitis or active, advanced disease in whom all other therapies have failed (5).

Two recent developments in the drug treatment of rheumatoid arthritis represent important conceptual changes in cytotoxic drug therapy for rheumatic diseases. Clear evidence now suggests that functional disability and radiographic changes develop most rapidly during the first several years of rheumatoid arthritis (6, 7). As a consequence, cytotoxic drugs are introduced early, often at the time of diagnosis in patients at risk for progressive disease. Markers that have been associated with a chronic, progressive course include genetic factors, high titers of rheumatoid factor, early functional impairment, development of subcutaneous nodules, and early radiographic abnormalities (8). In addition, drug combinations have been advocated on the premise that synergisms might result from disruptions of separate pathophysiologic pathways involved in synovitis. Recent studies of combinations of methotrexate with sulfasalazine (9-11), cyclosporine (12, 13), or biological agents (14) are promising and provide evidence that combination therapy is an important advance in the drug treatment of rheumatoid arthritis.

Systemic Lupus Erythematosus

Understanding of the immunopathogenesis of systemic lupus erythematosus almost exclusively derives from studies of lupus glomerulonephritis. The deposition of circulating autoantibodies or autoantibody-containing complexes along the endothelium of glomerular capillaries is believed to initiate complement-mediated inflammation with infiltration by immune cells, proliferation of glomerular capillary cells, thickening of the basement membrane, and scarring. Similar immunologic events are thought to be responsible for the abnormality seen in other organ systems affected in systemic lupus erythematosus, such as the skin, serous membranes, synovial tissues, and cutaneous and visceral blood vessels. The single exception is involvement of the central nervous system, which is the most clinically heterogeneous and least understood aspect of the disease.

Intravenous cyclophosphamide in systemic lupus erythematosus has been best studied in lupus nephritis, for which controlled trials have shown clear evidence of efficacy (see discussion by Dr. Balow). An increasing number of case reports and case series have described clinical benefits of bolus cyclophosphamide in lupus that affects other major systems or organs, including the central nervous system (15, 16), lungs (17, 18), and arteries (19). It seems unlikely that controlled trials for these indications will be forthcoming given the rarity of these manifestations and the difficulties of designing trials with clear end points for these heterogeneous conditions.

Both azathioprine and, more recently, weekly methotrexate (20) are effective in the treatment of lupus manifestations not affecting major organs, including rashes, serositis, and arthritis, or as adjuncts to allow reduction in glucocorticoid dose. The experience with cyclosporine in nonrenal manifestations of systemic lupus erythematosus is limited, although clinical benefits have been reported (21).

Inflammatory Myopathies

A spectrum of inflammatory muscle syndromes differs both in clinical features and in pathologic findings; polymyositis, dermatomyositis, and inclusion-body myositis are the most common of these syndromes. Polymyositis and inclusion-body myositis seem to result from cell-mediated, antigen-specific cytotoxicity, whereas humoral immune mechanisms seem to underlie the abnormality of dermatomyositis (22). Vasculitis is a particularly prominent feature of juvenile dermatomyositis.

The literature on cytotoxic agents in various forms of inflammatory muscle disease consists almost entirely of case series; only azathioprine has been shown to be beneficial in a randomized, controlled setting (23). Low-dose weekly methotrexate or azathioprine, along with high-dose glucocorticoids, has become the standard of initial drug treatment in both polymyositis and dermatomyositis (24); preliminary data suggest a role for combinations of methotrexate with azathioprine (25) or cyclosporine (26) in treatment-resistant disease. In addition, low-dose methotrexate has been reported to be beneficial in the management of the cutaneous features of dermatomyositis (27).

Although not well studied, intravenous cyclophosphamide has been reported to have little effect on the course of myositis (28). It may, however, have a role in the treatment of the severe interstitial pneumonitis that commonly accompanies the disease (29, 30). Similarly, the experience with cyclosporine in the inflammatory myopathies is limited, although the evidence of efficacy in adults (31) and, in particular, children with dermatomyositis (26, 32) seems promising. Finally, although inclusion-body myositis is generally considered the myositis syndrome that is the least responsive to treatment, clinical improvements with cytotoxic drugs have been documented (33).

Scleroderma

The pathogenesis of scleroderma involves a complex and poorly understood pathway involving small-vessel vasculopathy, autoimmunity, and fibrosis. The widespread fibrosis caused by the deposition of collagen, fibrinectin, and glycosaminoglycans by acti-
vated fibroblasts seems to be a cytokine-mediated response to either immune events or endothelial injury. Fibrosis is irreversible; this argues for early intervention in the disease with agents directed at immune suppression, endothelial cell damage, or both.

In controlled trials, chlorambucil and 5-fluorouracil did not modify the course of skin disease in scleroderma (34, 35). Although case reports have described benefits of cyclosporine in scleroderma (36), the potential for drug-induced nephrotoxicity and recent reports of the precipitation of scleroderma renal disease in association with cyclosporine treatment (37) indicate a need for caution. The role of methotrexate in scleroderma has not been well studied, but improvements in skin scores and general well-being were reported in a placebo-controlled study (38). Perhaps most important, several studies have suggested an important role for bolus intravenous cyclophosphamide in the treatment of interstitial pneumonitis in scleroderma (39-41).

**Table 2. Effects of Cytotoxic Drugs in Selected Immunologically Mediated Glomerular Diseases***

| Disease                                | Treatment                                                                                      | Remission or Control |
|----------------------------------------|------------------------------------------------------------------------------------------------|
| Minimal-change nephropathy             | Cyclophosphamide or chlorambucil for 2–3 months after glucocorticoid-induced remission of the nephrotic syndrome is effective in reducing the rate of relapse; trial of cyclosporine has limited value for glucocorticoid-resistant and cytotoxic drug-resistant nephrotic syndrome |
| Goodpasture disease                    | Cyclophosphamide plus plasmapheresis is used to control pulmonary hemorrhage and rapidly progressive glomerulonephritis and to reduce the titer of anti-GBM antibody; cyclophosphamide is usually continued until clinical remission of active nephritis has occurred and patient is negative for anti-GBM antibody for several months |
| ANCA-positive glomerulonephritis       | For induction, use cyclophosphamide until clinical improvement; for maintenance, consider switching to azathioprine, methotrexate, or intravenous cyclophosphamide |
| Idiopathic membranous nephropathy      | Alternating monthly cycles (three each) of intravenous pulse methylprednisolone and chlorambucil are effective in reducing proteinuria and stabilizing renal function; long-term cyclophosphamide therapy (for example, 1–2 years) is also effective but is limited by toxicity; cyclosporine reduces proteinuria but requires continued therapy (intravenous cyclophosphamide is not effective) |
| Lupus nephritis Proliferative          | Short-term (6 months) cyclophosphamide therapy or monthly intravenous cyclophosphamide therapy is beneficial but has high rates of relapse; intravenous cyclophosphamide monthly for 6 months, then quarterly for 1 year beyond sustained remission produces best long-term stability |
| Membranous                             | Intravenous cyclophosphamide therapy on alternate months produces high rate of sustained remission of the nephrotic syndrome; options for idiopathic membranous nephropathy are also effective |

* ANCA = antineutrophil cytoplasmic antibody; GBM = glomerular basement membrane.

**Summary**

Cytotoxic drugs and cyclosporine play an important role in the treatment of the major systemic inflammatory rheumatic diseases. Low-dose methotrexate for rheumatoid arthritis, intravenous cyclophosphamide for major organ disease in systemic lupus erythematosus, and interstitial fibrosis in scleroderma and inflammatory myopathies are examples of important advances that have diminished the morbidity and mortality rates associated with rheumatic disorders. In rheumatoid arthritis, the introduction of these agents early in the disease course, as well as combination therapy, represents important changes in treatment philosophy that merit further study in other rheumatic diseases.

**Renal Diseases, Including Lupus Nephritis**

Dr. James E. Balow (National Institute of Diabetes and Digestive and Kidney Diseases, NIH): Substantial progress has been made in the past 25 years in the management of several forms of immunologically mediated renal disease (42). To illustrate the utility of cytotoxic drugs in this regard, I have selected examples of glomerular disorders arising from the following putatively distinct pathogenetic mechanisms: 1) toxic soluble mediators causing altered glomerular permeability, illustrated by minimal-change nephrotic syndrome; 2) direct IgG antibody-mediated tissue injury, illustrated by Goodpasture disease; 3) antineutrophil cytoplasmic antibody (ANCA)-associated vascular injury, illustrated by microscopic polyangiitis and Wegner granulomatosis; and 4) two forms of immune complex deposition, illustrated by membranous nephropathy (possibly in situ-formed immune complexes) and lupus nephritis (circulating immune complexes). The effects of cytotoxic drugs and cyclosporine on these selected forms of immunologically mediated glomerular diseases are summarized in Table 2.

**Minimal-Change Nephropathy (Lipoid Nephrosis, Nil Disease)**

As the name implies, this common cause of idiopathic nephrotic syndrome shows few, if any, cellular changes; no immune deposits; and no inflammation in glomeruli. Ultrastructurally, there is fusion of foot process of glomerular epithelial cells that correlates with heavy albuminuria. Evidence that toxic circulating lymphokines neutralize the normal glomerular barrier to protein filtration is fragmented and controversial. However, the characteristic exquisite sensitivity of the nephrotic syndrome of minimal-change disease to glucocorticoids, cyclosporine, and alkylating agents make disordered lymphoid cell function an attractive hypothesis for the pathogenesis of this glomerular disease (42, 43).
Progressive renal insufficiency is uncommon in minimal-change nephropathy. The major clinical problems are the morbidity incurred by frequently relapsing nephrotic syndrome and the need for repetitive or sustained glucocorticoid treatment. Several controlled clinical trials conducted since the 1970s have proven the benefit of 2- to 3-month courses of oral cyclophosphamide (or chlorambucil) in patients with frequently relapsing minimal-change nephropathy; of note, azathioprine has not proven efficacious. In various controlled studies, the probability of sustained remission after a course of cyclophosphamide has been two to four times higher than that after therapy with glucocorticoids alone (44–47). Cyclophosphamide is also effective in the occasional patient with minimal-change nephropathy who is resistant to glucocorticoids (48). A small controlled trial involving patients with glucocorticoid-resistant minimal-change nephropathy suggested that intravenous pulse cyclophosphamide was more efficacious than conventional daily cyclophosphamide (49). Although pulse cyclophosphamide may offer less cumulative toxicity, additional studies are needed before this method is accepted for treatment of frequently relapsing or glucocorticoid-resistant minimal change disease. Low-dose cyclosporine has been found to be another effective option for frequently relapsing minimal-change nephropathy (less so for glucocorticoid-resistant disease). However, sustained treatment is usually necessary because the nephrotic syndrome tends to recur after cyclosporine therapy is discontinued (47, 48, 50).

**Goodpasture Disease**

Although rare, Goodpasture disease is one of the clearest examples of autoimmune pulmonary-renal syndromes (42, 51). Autoantibodies are directed toward the collagenuous components of the basement membranes of the kidney and lung. Clinical diagnosis is based on pulmonary hemorrhage and crescentic glomerulonephritis caused by linear deposition of IgG antibody along capillary basement membranes. High-dose glucocorticoids, including pulse methylprednisolone, are the mainstay of immediate therapy for both the pulmonary and the renal components of Goodpasture disease. However, the production of pathogenic anti-basement membrane antibodies must be reduced with a combination of plasma exchange and cyclophosphamide therapy. A controlled trial has proven that plasma exchange accelerates the rate of decline of the production of circulating antiglomerular basement membrane antibodies compared with that achieved by cyclophosphamide alone (52). Cyclophosphamide is considered essential in reducing the production of anti-basement membrane antibodies, although this has not been proven in controlled trials. There is consensus that standard daily cyclophosphamide therapy should be continued for several months after clinical remission of Goodpasture disease has occurred and the patient has become negative for anti-basement membrane antibody titers (51).

**Renal Vasculitis**

Vasculitic diseases are common causes of the pulmonary-renal syndrome and are the most common cause of necrotizing and crescentic glomerulonephritis (53, 54). From the perspective of pathogenesis, it is provocative that the renal vasculitides usually have scant, if any, immune reactants (antibody and complement) in sites of active pathology. The discovery of ANCA in patients with Wegener granulomatosis and microscopic forms of polyarteritis (polyangitis) has been a boon for diagnosis and has offered a new hypothesis for the pathogenesis of these conditions. It is proposed that ANCA-activated neutrophils mediate the vasculitic injury, particularly in the kidney, where the presence of ANCA is strongly correlated with necrotizing, crescentic glomerulonephritis; however, this is controversial. On the other hand, there is less convincing information that ANCA titers correlate well with the severity or activity of the glomerular disease, thus limiting the utility of ANCA measurements as a guide to therapy.

As they are with most other immunologically mediated renal diseases, glucocorticoids are crucial in the initial stages of severe inflammation. However, it has been known for decades that cytotoxic drugs are needed for successful treatment of the renal diseases of Wegener granulomatosis and microscopic polyangitis, although several controversial issues remain. There is consensus that among cytotoxic drugs, cyclophosphamide provides the most substantial benefit for the renal and systemic components of these vasculitic diseases. However, the cumulative toxicity of sustained courses of standard daily cyclophosphamide has prompted a continued search for alternative regimens. Although early experience, particularly in Wegener granulomatosis, indicated that pulse cyclophosphamide was less satisfactory than standard daily cyclophosphamide in achieving sustained remission (see discussion by Dr. Sneller, in part 2 of this paper), some have claimed that pulse cyclophosphamide therapy is as effective as standard therapy for treatment of these renal vasculitides (54, 55). Cyclosporine has not proven substantially beneficial in the vasculitic diseases.

**Membranous Nephropathy**

Membranous nephropathy is associated with heavy deposition of immune complexes along the outer surface of the glomerular basement membrane (56).
Indeed, given the differences in natural history and responses to treatment, it seems likely that different mechanisms may be operant in primary and secondary forms of membranous nephropathy.

The indications for treatment of membranous nephropathy are controversial (57). On the one hand, membranous nephropathy leads to end-stage renal failure in about one quarter of patients older than 15 years of age. On the other hand, substantial atherosclerotic and thromboembolic risk due to protracted nephrotic syndrome was recently suggested as an additional rationale for therapeutic intervention in membranous nephropathy (58). Attempts to identify particular factors associated with high risk for progression continue; this information would be extremely useful in defining indications for treatment of membranous nephropathy.

Glucocorticoids are routinely used to treat idiopathic membranous nephropathy, although there is little support for an enduring benefit on the basis of controlled therapeutic trials. Several forms of cytotoxic drug therapy have been tested, and meta-analysis has concluded that they confer clear benefits (57). A series of studies from Italy conducted since the early 1980s have shown that a total of 6 months of alternating monthly pulse methylprednisolone and daily chlorambucil confers a higher probability of remission and stabilization of renal function than do glucocorticoids alone (59, 60). Other studies using sustained daily cyclophosphamide (61) or cyclosporine (62) have also shown benefit over glucocorticoids alone. Of note, one published report (63) and our own preliminary results of a controlled trial failed to show a benefit of pulse cyclophosphamide in idiopathic membranous nephropathy. In a parallel trial involving lupus membranous nephropathy, our preliminary results indicate that both pulse cyclophosphamide and cyclosporine are more effective than glucocorticoids alone in achieving remission of proteinuria. Relapses after discontinuation of treatment seem to occur more frequently with cyclosporine than with pulse cyclophosphamide (64).

Lupus Nephritis

Proliferative forms of lupus nephritis are associated with deposits of immune complexes in the mesangium and beneath the endothelial cells that line the glomerular capillaries. By acclamation, glucocorticoids are recognized for their salutary effects on numerous systemic components of lupus. Gathering proof that cytotoxic agents add substantially to glucocorticoids has been an arduous and incremental process involving a series of controlled clinical trials conducted since the early 1970s. Short-term (6 months) cyclophosphamide therapy was more effective than prednisone alone in controlling the activity of lupus nephritis (65), but the late risk for end-stage renal failure was not diminished by the brief period of cyclophosphamide therapy. In contemporary studies at the NIH, longer courses of cytotoxic agents were used until patients achieved sustained remission. These studies showed that cytotoxic drug regimens containing cyclophosphamide were better than glucocorticoids alone in controlling clinical and serologic activity of lupus; in protecting against progressive renal histologic damage; and, ultimately, in reducing the risk for end-stage renal failure (66). Azathioprine was not substantially better than prednisone alone in preventing these outcomes. Subsequent trials did not study regimens that contained oral cyclophosphamide because pulse cyclophosphamide had the best therapeutic index. Two subsequent clinical trials involving proliferative lupus nephritis compared pulse methylprednisolone with pulse cyclophosphamide (67, 68). In neither study was pulse methylprednisolone as effective as pulse cyclophosphamide in preserving renal function or in achieving remission of nephritis. Continuing pulse cyclophosphamide for at least 1 year after achievement of stable remission of lupus nephritis was associated with decreased probability of subsequent nephritic flares, which are recognized predictors of adverse renal outcome (69), A detailed review of the treatment of lupus nephritis was recently published (70).

References


