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New Therapeutic Approach of Retinoids for Lupus Nephritis

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Introduction

Lupus nephritis is a major cause of morbidity and mortality in patients with Systemic Lupus Erythematosus (SLE) [1]. Nephritis may then progress to a chronic phase, characterized by excessive deposition of collagen and other extracellular matrix macromolecules [2]. Lupus nephritis is also believed to result mostly from renal deposition of autoantibodies and immune complexes [3], which in turn triggers an acute inflammatory response characterized by activation of leukocytes and renal parenchymal cells. This activation is accompanied by the production of cytokines and growth factors. The glomerulus is one of the sites most seriously affected, with tissue damage progressing to end-stage renal disease in as much as 30% of patients. Although various functional disturbances within tissues have been implicated in the pathogenesis of SLE, details of the initiating events and accompanying detrimental processes on both systemic and end-organ levels remain largely unknown. Current therapies, such as corticosteroids, cyclophosphamide and azathioprine, are largely cytotoxic in nature and are associated with undesirable side effects. More targeted therapies aimed at depleting or modulating the activity of pathogenic lymphocytes may represent a more effective and safer alternative. For example, approaches, such as treatment with a monoclonal antibody against the B cell growth factor, B-lymphocyte stimulator [4], or depletion of B lymphocytes with Rituximab [5], are currently being tested. However, these agents have severe potential side effects, including increased susceptibility to infections and the development of malignant tumors [6]. Therefore, the development of new drugs with few side effects is needed in the patients.

Retinoids are a group of natural and synthetic derivatives of vitamin A that exert antineoplastic and immunomodulatory actions and they have been used for the treatment of acute promyelocytic leukemia [7] and such inflammatory disorders as psoriasis [8], acne [9] and rheumatoid arthritis [10]. Recently, we reported retinoids showed excellent therapeutic efficacy in human lupus nephritis [11]. Retinoids also improve renal pathological findings and proteinuria in various animal models of kidney disease. Retinoid treatment can prevent proteinuria by protecting renal injury and diminishing leukocytes infiltrating in lupus model mice [12]. Furthermore, retinoids prevent renal interstitial fibrosis in the unilateral ureteral obstruction model [13]. These studies also suggest that retinoids could be a promising new medication for treatment of lupus nephritis. The goal of each of treatments has been to achieve clinical efficacy by inducing a remission of the nephritis while at the same time minimizing severe side effects of treatment. This review article focuses on the potential advantages of retinoids treatment in lupus nephritis.

Pathogenesis

SLE is an autoimmune condition characterized by the development of autoantibodies against various cellular components, most notably dsDNA, a hallmark of the disease. The pathogenesis of the disease is not fully understood but appears to involve defects in the activity of regulatory T cell (Treg) [14] and abnormal activation of auto reactive B and T lymphocytes [15]. The histological presentation and patterns of glomerular injury in lupus nephritis are heterogeneous, with varying involvement of mesangial and vascular elements. An invariant finding, however, is the accumulation of immune complexes within glomerular membranes, which is often accompanied by an apparent expansion of vascular and /or mesangial extracellular matrices as the disease progresses. Autoantibodies against dsDNA are considered to be an important factor in the evolution of lupus nephritis. Several nephritogenic anti-dsDNA antibodies appear to bind DNA in the form of nucleosomes and extracellular chromatin has been found to colocalize with such antibodies in situ [16]. Recent data demonstrated considerable affinity of nucleosomes for collagen IV [16]. Increased production or reduced degradation of collagen IV might theoretically contribute to accumulation of extracellular chromatin, thus maintaining or aggravating autoantibody deposition. The causes underlying the observed glomerular basement membrane thickening are unknown, but it has been speculated that increased synthesis or decreased turnover of extracellular matrix constituents such as collagen IV might be contributing factors [16].

Recently, there have been several reports that abnormalities of both the Th1 and Th2 cells are associated with the pathogenesis of autoimmune disorders [17,18]. Among the Th1 cytokines IFN-γ, the production of which is promoted by IL-12, plays a key regulatory role in the development of autoimmune kidney diseases and deletion of IFN-γ receptor or IFN-γ genes or administration of anti-IFN-γ monoclonal antibody improved the survival rate of lupus-prone mice [19–22]. IL-12 has been reported to promote T cell proliferation [23] and differentiation of CD4+ T cells into Th1 cells [24] and its production by tubular epithelial cells and macrophages is up-regulated along with the development of lupus nephritis in MRL-Fas^{lpr} mice [25,26]. Among the Th2 cytokines, IL-4 enhances the differentiation of both B cells and T cells (especially Th2 cells) and increased production of IL-4 is also associated with the pathogenesis of SLE [27] and lupus nephritis [28]. Development of kidney disease is one of the most serious consequences of SLE.

Current Agents for the Treatment of Lupus Nephritis

Cyclophosphamide

Cyclophophamide is given as intravenous pulses to achieve remission in severe SLE and lupus nephritis. The modified National Institute of Health protocol of 6 monthly intravenous pulses of cyclophosphamide at 0.5–1 g/m^2 with dose reduction in renal failure,

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with 3-monthly pulses thereafter, is normally reduced because of the short- and long-term side-effects, such as haemorrhagic cystitis (with mesna given with additional fluids for prophylaxis), neutropenia and infectious complications, nausea, alopecia, amenorrhoea and infertility. Despite protective measures, there are significantly more side-effects with cyclophosphamide, including severe infections compared with oral azathioprine or MMF [29-32]. Patients require blood tests at around 7–10 days after infusions to monitor the safety and efficacy of treatment with total white cell, neutrophil and lymphocyte counts with subsequent dosing based on hematological results. Amenorrhea, infertility and malignancy risks are increased with cyclophosphamide [33].

Mycophenolate mofetil

MMF effectively and selectively suppresses T and B lymphocyte proliferation, antibody production and expression of proinflammatory adhesion molecules on lymphocytes [34]. It was initially administered to prevent acute rejection of renal allografts [35] but is currently also applied in the treatment of primary glomerulonephritis and lupus nephritis [36]. MMF has been used for induction and maintenance treatment, especially in patients with severe lupus nephritis, those with lupus nephritis refractory to cyclophosphamide and subjects who cannot tolerate cyclophosphamide.

Tacrolimus

Tacrolimus is a macrolide calcineurin inhibitor that potently suppresses human T-cell proliferation by inhibiting the intranuclear translocation of cytoplasmic nuclear factors in activated T cells by binding to tacrolimus-binding proteins and inhibiting calcineurin. Compared with cyclosporine, it seems more prospective in prevention of transplant rejection and is associated with less hypertensive and adverse cosmetic effects. Early anecdotal experiences suggest that tacrolimus could be a treatment option for patients with lupus and topical tacrolimus has been used in the treatment of lupus dermopathy [37]. However, the side effects of tacrolimus such as diabetogenesis and nephrotoxicity remain valid concerns. Little evidence of randomized controlled trials has been published on the efficacy and safety when administered with corticosteroids treatment of lupus nephritis.

New agents for the Treatment of Lupus Nephritis

Rituximab

Rituximab is a chimeric antibody directed against CD20, a phosphoprotein expressed on almost all B cells but not on plasma cells. Therefore, through the elimination of B cells rituximab may prevent the generation and expansion of antibody-secreting autoreactive cells [38]. Using rituximab to deplete B cells may have the advantage of being generally well tolerated and to spare T cells and plasma cells, which are CD20-negative [39]. However, double-blind controlled trials are advocated to confirm its role in lupus nephritis and to find whether rituximab alone may be effective or should be associated with other drugs and, in the latter case, what the combination that offers the best therapeutic index is. Until these data are available, the use of rituximab should be confined to cases resistant to standard induction therapy or to patients with contraindications to corticosteroids and immunosuppressive agents.

Belimumab

Belimumab binds soluble B-lymphocyte stimulator B-cell activating factor, which is a member of the tumor necrosis factor family and a cytokine that is essential for B-cell growth, differentiation and survival. Belimumab inhibits the factor's biological activity [40]. A study of belimumab in SLE patients (BLISS-52 and BLISS-76) showed that it improved the clinical symptoms, serological profiles and markers of renal function, as well as prevented SLE flares [41]. In addition, belimumab was found to be well tolerated.

Abatacept

Abatacept is a selective T-cell costimulation modulator that has been approved for use in adult rheumatoid arthritis and juvenile idiopathic arthritis. T-cell activation, a crucial step in the pathogenesis of glomerulonephritis, requires both binding of the T-cell receptor to the antigen–major histocompatibility complex on the antigen-presenting cell and a costimulatory signal provided by binding of the CD28 protein (on the T cell) to the B7 protein (on the antigen presenting cell). Abatacept binds to the B7 protein, thereby preventing this costimulatory signal and, in turn, preventing activation of T cells [42]. Two current clinical trials are exploring the use of abatacept in lupus nephritis as add-on induction phase therapy to the Euro-Lupus cyclophosphamide regimen or MMF [43].

Retinoids

Vitamin A and its metabolites: The term retinoids is applied to a family of compounds that bind to and activate retinoic acid receptors (RARs and RXRs), resulting in a range of possible biological responses. Some natural retinoids, such as ATRA (Tretinoin), 9-cis RA (Alitretinoin) and 13-cis RA (Isotretinoin), are currently already used in the clinic. As the clinical use of natural retinoids is limited by their pharmacological profile, including instability, poor bioavailability and the possible side effect due to the nonspecific receptor binding of those natural retinoids, a number synthetic retinoids have been generated. These include mono-aromatic synthetic retinoids (second generation), such as Tamibarotene (Am80), Tazarotene and Targretene (LGD1069) (Table 1). The aromatic rings found in the second and third generation retinoids confer a higher stability and resistance to heat/oxidation, increased half-lives, a higher potency and improved spectrum of action with receptor specificities.

The first group are natural provitamin A, vitamin A and other RA precursors, which cannot bind retinoid nuclear receptors, but are characterized by their potential to be converted into retinoids; the second group includes the natural retinoids, including ATRA and 13-*cis*-RA, which bind and activate RARs and 9-*cis*-RA, which binds and activates both RARs and RXRs.The third group is composed of synthetic retinoids, which bind one or more RAR or/and RXR isotypes and exert agonistic or antagonistic actions. Some of the third group activate neither RARs nor RXRs, but have selective anti-activator protein-1 activity [44]. Although vitamin A does not bind any of the nuclear receptors, the majority of its functions are retinoid nuclear receptor–dependent; therefore, conversion of vitamin A into RAs that

Name	Receptors	Clinical use
ATRA	pan-RAR	APL, Acne
9-cis RA	pan-RAR, pan-RXR	Kaposi sarcoma
13-cis RA	-	Acne
Etretinate	-	Psoriasis
Acitretin	pan-RAR	Psoriasis
Tamibarotene	RARα/β»γ	APL
Tazarotene	RARβ/γ»α	Acne
Targretin	pan-RXR	Cutaneus T lymphoma

Table 1: Categorization of Retinoids

can bind retinoid nuclear receptors is largely a process of vitamin A activation [44].

Effect of RA on cytokines and modulating T regulatory cell differentiation: Recent studies have shown that RA, in concert with TGF-β, has ability to induce Foxp3 (forkhead box 3) in CD4+ T cells [45,46]. Foxp3+ CD4+ Treg cells play a pivotal role in the maintenance of dominant self tolerance and lack of functional Treg cells is associated with various autoimmune diseases. A recent study has shown that the decreased frequency of Treg cells in the peripheral blood was associated with disease activity in SLE patients [47]. Specific subsets of intestinal antigen presenting cells have the capacity to produce RA and induce to Foxp3+ Treg in vitro, in the presence of TGF-β [45,46]. Foxp3+CD4+ cells are reciprocally linked with the development of Th17 effector cells 6, 7 and recent studies suggest that these Foxp3+ Tregs cells can regulate both Th1 and Th17 mediated effector responses. In experimental murine glomerulonephritis, both Th1 and Th17 effector subsets and their respective signature cytokines, IFN-γ and IL-17A, can mediate severe glomerular disease [48-50]. In addition to its role in inducing T regulatory cells, accumulating evidence suggest RA, at high concentrations, suppresses Th1 and Th17 differentiation by suppressing the lineage specific transcription factors and also by suppressing the expression of effector cytokines IFN-γ and IL-17 [51].

Potential Advantages of Retinoids in Lupus Nephritis

Recently, RA, a family of vitamin A metabolites or analogs, have been shown to have excellent preventive and therapeutic effects in various experimental kidney diseases, as shown in Table 2 [11,13, 28,52-60]. RA might prove useful in the treatment of various renal conditions, some of which, such as hypertensive nephropathy, focal-segmental glomerulosclerosis, pyelonephritis and renal interstitial fibrosis, are contraindicated in the use of glucocorticoids. One of the most important adverse effects of glucocorticoids and cytotoxic agents is the risk of infection. In contrast, as shown in Table 2, RA have been used in both infective and non infective renal inflammation and have rarely been reported to induce severe acquired infection in patients. This might be due to the fact that the effect of RA on immunity is "immune modulation" rather than a nonspecific "immune suppression". Emerging evidence indicates that, although RA is potent anti-inflammatory agents, they may also have proinflammatory potential by inducing some proinflammatory molecules. For example, RA can induce inducible nitric oxide expression in vivo [61] and enhance IL-8 [62] and intercellular adhesion molecule-1 [63] expression in vitro. Further, since ATRA has been shown to potentiate tubulointerstitial nephritis both in patients and in animal models [11,27]. We previously reported that ATRA treatment in SLE–prone New Zealand Black/White F1 mice significantly alleviates autoimmune renal disorder and prolongs survival.6 In that report, we showed that ATRA inhibits IFN-γ expression, leading to decreased immunoglobulin G2a anti-DNA antibody production and immunoglobulin G2a deposition in glomeruli and results in the prevention of fatal autoimmune kidney disease in New Zealand Black/White F1 mice. Furthermore, ATRA has the potential to act as a steroid-sparing drug against lupus nephritis [64]. The mechanisms by which retinoids improve lupus nephritis are difficult to elucidate because retinoids have potent antiproliferative and antiinflammatory effects. For example, treatment with retinoids can ameliorate renal injury in anti-Thy1.1-nephritis rat models by reducing proliferating cell nuclear antigen–positive cells, platelet derived growth factor B-chain and transforming growth factor [65-67]. In addition, retinoid treatment can prevent proteinuria by protecting podocytes from injury and diminishing infiltrating cells in puromycin aminonucleoside nephrosis rat models [54]. Retinoids also attenuate inducible nitric oxide synthase, which causes oxidative injury in glomerulonephritis [61]. Furthermore, retinoids prevent renal interstitial fibrosis in the unilateral ureteral obstruction model [13]. We also report a dramatic therapeutic response to ATRA in 2 patients with lupus nephritis [11]. ATRA treatment rapidly improved clinical symptoms and laboratory findings, including urinary protein and anti–ds-DNA antibody levels of these patients. In both patients, ATRA was administered for 6 months and stopped after complete remission was achieved. Thus, RA might be indicated in cases of lupus nephritis that are refractory to conventional immunosuppressive therapy.

Model	Response to RA	Reference
Acute Thy1.1 nephritis	+	52
Chronic Thy1.1 nephritis	+	53
Puromycin aminonucleoside nephrosis	+	54
Lupus nephritis	+	11, 28
Acute kidney allograft rejection	+	55
Aging related nephropathy	+	56
Unilateral ureteral obstruction	+	13
Pyelonephritis	+	57
Anti-GBM nephritis (chronic phase)	+	58
Anti-GBM nephritis (acute phase)	±	59
Radiation nephritis	-	60

Note: +, renal damage reduced; ±, proteinuria unchanged; -, renal damage enhanced

Table 2:Effects of retinoic acid on animal models of renal disease

Conclusion and Perspectives

RA target mesangial cells, podocytes, tubular epithelial cells, interstitial fibroblasts, as well as T lymphocytes and macrophages and have antiinflammatory, anticoagulatory, antifibrotic effects and proliferation- and immunity-modulating actions. All these features make RA a promising new generation of renal medication for use in lupus nephritis of renal diseases. The pharmacologic effects of RA reported in animal studies suggest that it may be worthwhile to examine whether RA can be useful in dealing with the following conditions of lupus nephritis (1) steroid-resistant glomerulonephritis, such as focal segmental glomerulosclerosis, membranous nephropathy and membranous proliferative glomerulonephritis; (2) glomerulonephritis responsive to but developing secondary resistance to steroids, such as refractory minimal change nephrosis, mesangioproliferative glomerulonephritis; (3) glomerulonephritis with mild to moderate chronic renal failure and renal fibrosis; (4) glomerulonephritis complicated by diabetes or other side effects of steroids; (5) crescentic glomerulonephritis; (6) renal transplantation.

Here we describe the agents of the treatment in lupus nephritis. The goal of treatments has been to achieve clinical efficacy by inducing a remission of the nephritis while at the same time minimizing severe side effects. Retionoids have many immunomodulatory actions while it has no severe side effects. Retinoids could be a promising new medication for treatment of lupus nephritis.

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