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ACD40-CD40L Co-Stimulatory Pathway: A Promising Immune-Therapeutic Target in Systemic Lupus Erythematosus

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Abstract:

Therapeutic approaches for the treatment of lupus nephritis and systemic lupus erythematosus have emerged from the inhibition of the CD40-CD40L pathway. Early-phase clinical trials and preclinical studies have underlined the efficacy of this approach by showing declines in renal inflammation, autoantibody concentrations, and proteinuria, so indicating changes in important disease markers. Second-generation anti-CD40 and anti-CD40L antibodies including BI 655064, Iscalimab, and Dapirolizumab pegol offer a safer and more effective treatment alternative that has lessened safety concerns about thromboembolic events recorded in past treatments. These new molecules are meant to be more selective targets, so reducing undesired immune response. The results of present Phase II studies will be very important in deciding whether these treatments are safe and effective for SLE and LN patients. Should these treatments be successful, they could considerably slow down development, improve long-term patient outcomes, lower renal damage, and greatly improve disease management. The therapeutic possibilities of CD40-CD40L blockage as well as their ability to transform lupus treatment are investigated in this review.

Keywords: Systemic Lupus Erythematosus, Lupus Nephritis, CD40-CD40L pathway, autoimmune diseases, monoclonal antibodies.

Introduction

The chronic autoimmune disorder known as systemic lupus erythematosus breaks down self-tolerance and produces autoantibodies aimed at nuclear antigens (1, 2). Renal involvement in SLE, sometimes referred to as lupus nephritis (3), affects 40–60% of patients and is a major cause of end-stage renal disease; approximately 10% of patients advance to this stage within a decade (4). LN significantly elevates morbidity, mortality, and the overall health burden in affected individuals. Maintaining renal function, preventing disease exacerbations, lowering treatment-associated adverse effects, and improving the patient's quality of life are the main objectives in controlling LN. Usually, treatment consists in strong immunosuppressive induction phase therapy followed by maintenance therapy (5). Often taken in combination with glucocorticoids, common medications include cyclophosphamide, azathioprine, and mycophenolate mofetil (MMF). Rituximab, an

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anti-CD20 monoclonal antibody, is occasionally utilized for patients who do not react to traditional treatments or suffer from significant adverse effects, despite its lack of formal indication for LN (7). Though survival rates have improved over the past thirty years, these treatments have been linked to significant side effects including ovarian failure, leukopenia, alopecia, and increased susceptibility to infections (8, 9). Extended glucocorticoid use could cause ocular damage, steroid-induced diabetes, low bone mineral density, and Cushingoid symptoms (10). Treatment failure and refractory lupus nephritis are much influenced by non-compliance resulting from these negative consequences. As such, more effective and better-tolerated treatments especially addressing the basic processes of LN are desperately needed (11, 12).

In parallel, the CD40-CD40L signaling pathway has emerged as a critical mediator in various autoimmune and inflammatory diseases, including SLE and atherosclerosis (13). Working within the tumor necrosis factor receptor and ligand superfamily, co-stimulating molecules CD40 and CD40L are essential for activating the adaptive immune response (14). Research over the past thirty years has clearly shown that the CD40-CD40L system drives immune responses in these disorders (15). Nevertheless, the precise biological purpose of this pathway is still a subject of discussion, so complicating our whole knowledge of its influence (16). Advancement of vascular inflammation in atherosclerosis, a chronic inflammatory disease of the arterial walls, depends on interactions between antigen-presenting cells (APCs) and T lymphocytes (17). The immunological processes of SLE and atherosclerosis will be investigated in this review together with the function of CD40-CD40L in their development and progression as well as therapeutic approaches meant to target this pathway to reduce disease outcomes in both diseases (18).

Given the critical role the CD40-CD40L pathway plays in atherosclerosis and systemic lupus erythematosus, targeted modulation of this pathway offers possible therapeutic advances to fill in for current shortcomings in both diseases (19). By means of a more exact and less toxic approach for altering immune responses in systemic lupus erythematosus, lupus nephritis, and atherosclerosis, targeting CD40-CD40L interactions may help to improve patient outcomes and minimize long-term therapy consequences (20).

The biological function of CD40-CD40L interaction

Adaptive and innate immune responses depend on the CD40-CD40L interaction. Signalling that modulates many immunological processes is started by the interaction between CD40 on immune cells including B cells, dendritic cells, and macrophages, and CD40L on T cells. B cell differentiation, proliferation, and memory B cell development depend on the interactions between CD40 and CD40L (22). The connection also helps T cell-dependent immune responses, which include the development of germinal centers, changing immunoglobulin classes, somatic hypermutation, and the formation of plasma cells. This route is essential in thymus-dependent immunological responses, wherein the activation of helper T cells (Th) and T follicular helper (TFH) cells is pivotal for B cell activation (24). By increasing cytokine production, boosting co-stimulating molecule expression, and encouraging Th-cell proliferation, the interaction of CD40 and CD40L influences dendritic cell functions (25).

Apart from its role in humoral immunity, especially in autoimmune diseases, the CD40-CD40L pathway helps cell-mediated immunity (26).

This link can increase the expression of CD80/86 on dendritic cells, which triggers T cells associated with graft rejection. Inhibition of CD40 or CD40L can trigger T cell death and facilitate the differentiation of regulatory T cells (27). Additionally, by modulating macrophage activation, this pathway produces matrix metalloproteinases, nitric oxide, and proinflammatory cytokines—all of which are vital for immunological responses (28). Furthermore indicating its function in vascular diseases, including atherosclerosis (29), the CD40-CD40L axis promotes adhesion between endothelial cells and neutrophils. Regarding lupus nephritis (3), understanding the role of CD40-CD40L in immune activation presents possible therapeutic directions. Biologic therapy, especially those targeting immunological pathways like CD40-CD40L, may reduce glucocorticoid utilization and renal flares in lupus nephritis (30). The main function of B cells in lupus nephritis and systemic lupus erythematosus has led to the creation of biologic treatments designed to manage B cell activity. Although rituximab (an anti-CD20 monoclonal antibody) is widely used for difficult cases of lupus nephritis, clinical trials have shown mixed results, and it is not yet approved for systemic lupus erythematosus or lupus nephritis. Alternative anti-CD20 antibodies, such as ocrelizumab and obinutuzumab, have undergone evaluation, with obinutuzumab demonstrating enhanced renal response when administered alongside standard therapy in a Phase IIb trial. Approved as an adjunctive therapy for systemic lupus erythematosus (2), belimumab is a human antibody that inhibits B-lymphocyte stimulator (BAFF), with Phase III studies in lupus nephritis showing positive results, including improvements in renal function and declines in proteinuria (33).

A major factor in the development of systemic lupus erythematosus and lupus nephritis is believed

to be the activation of the type I interferon (IFN) system. Evaluating an IFN receptor antagonist, anifrolumab, the Phase III TULIP 2 trial revealed a reduction in the severity of systemic lupus erythematosus disease activity, in line with the British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA). The Phase III TULIP 2 trial, which evaluated anifrolumab, an IFN receptor antagonist, showed a decrease in the severity of systemic lupus erythematosus disease activity, as per the British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) (2). Apart from drugs aimed at CD40 and its ligand, efforts have been made to target other co-stimulating molecules (35). Abatacept is a type of protein that connects CTLA4 to a part of immunoglobulin G1 (IgG1), mainly controlling the CD28–CD80/86 signaling pathway to prevent T-cell activation. Researchers have studied abatacept in lupus nephritis and systemic lupus erythematosus, despite its failure to meet its primary goals in many studies. Consequently, despite continuous and completed clinical trials, no biologic treatments have received a license for the treatment of LN (37).

CD40 antibodies and newer anti-CD40L antibodies were created to stop platelet activation and address previous safety issues, leading to renewed interest in this treatment approach for lupus nephritis. This study explains how CD40 and its ligand are involved in lupus nephritis and gives an overview of the CD40/CD40L-targeted therapies that are currently being developed.

CD40-CD40L and SLE

With its activation promoting inflammation and tissue damage in both diseases, the CD40-CD40L interaction is central in both atherosclerosis and lupus nephritis (39). The chronic inflammatory disease known as atherosclerosis, which affects the arterial walls, is typified by plaque development that narrows the arteries and causes severe consequences, including myocardial infarction, heart failure, and stroke (40). T cells and monocytes enter the injured vascular lining during its development, differentiate into macrophages, and help to create foam cells, so triggering additional recruitment of inflammatory cells and the breakdown of the extracellular matrix. Crucially in this process are CD40-CD40L interactions; CD40 expression on monocytes is essential in activating immune responses (41). This signaling pathway contributes to the formation of necrotic cores and plaque rupture, key events in cardiovascular events. Research on the inhibition of CD40-CD40L signaling in animal models has indicated that this could help to lower atherosclerotic plaque size and stabilize plaque phenotypes, so stressing CD40-CD40L as a possible therapeutic target for atherosclerosis (42).

In LN, too, key causes of renal inflammation and tissue damage are CD40-CD40L interactions. Severe form of systemic lupus erythematosus, LN, is typified by immune complexes deposited in the kidneys that activate renal cells and produce inflammatory cytokines and chemokines (43). This causes lymphocytes and myeloid cells to migrate, so aggravating tissue damage. Expression of CD40 is found in both immune and non-immune cells; its interaction with CD40L on T cells is essential for B cell activation and the synthesis of autoantibodies, so aggravating SLE and LN pathogenesis. In the kidneys, CD40L-mediated activation of mesangial cells, endothelial cells, and myeloid cells amplifies the inflammatory response, promoting fibrosis and glomerular injury (45). Key sources of CD40L, platelets help to upregulate CD40 on renal cells and generate pro-inflammatory molecules including MCP-1 and TGF-β1, so aggravating renal damage (46). Targeting the CD40–CD40L pathway seems to be helpful for treating LN since blockade of this pathway has been shown to lower MCP-1 generation and minimize glomerular damage.

Both atherosclerosis and LN are complicated inflammatory diseases in which tissue damage and immune cell activation depend critically on the CD40-CD40L interaction. While in LN CD40-CD40L signaling fuels renal inflammation and fibrosis, in atherosclerosis it helps to cause plaque instability and rupture. These insights underscore the potential of targeting CD40-CD40L interactions as a therapeutic strategy for both diseases, with ongoing research focusing on developing inhibitors of this pathway for clinical use (47).

Targeting the CD40-CD40L Pathway in Systemic Lupus Erythematosus (2) and Lupus Nephritis(3)

The CD40-CD40L pathway plays a key role in causing systemic lupus erythematosus and lupus nephritis. Starting and maintaining inflammatory processes in SLE, an autoimmune disease defined by systemic inflammation, dysregulated immune responses, and autoantibody generation, CD40-CD40L interactions between immune cells T cells, B cells, and dendritic cells are absolutely vital (48). This pathway generates autoantibodies and immune complexes that deposit in various tissues, including the kidneys, thereby accelerating the progression of the disease. This pathway also activates autoreactive T and B cells (49). Driven by kidney T cell and B cell activation (50), LN is one of the most severe SLE symptoms; hence, renal inflammation and damage result. Engaging on renal dendritic cells and other antigen-presenting cells, CD40L on activated T cells stimulates the synthesis of pro-inflammatory cytokines and

chemokines, aggravating tissue damage. Blocking the CD40-CD40L interaction seems like a good therapeutic strategy since it helps reduce immune-mediated damage and stops the development of end-stage renal disease (51).

Preclinical Models and Mechanistic Insights

Apart from the basic studies, several preclinical and clinical investigations have repeatedly looked at the therapeutic possibilities of CD40-CD40L blockage for lupus and lupus nephritis (52). Targeting the CD40-CD40L pathway has repeatedly been shown in studies both in human subjects and mouse models to reduce disease activity, improve renal function, and control immunological responses (53).

A study by Rush et al. (2014) investigated the therapeutic effects of anti-CD40 therapy in NZB/W-F1 mice with developed lupus nephritis (54). Anti-CD40 treatment reduced proteinuria, decreased autoantibody synthesis, and increased survival relative to control subjects, according to the study. Significantly, anti-CD40 therapy reduced histological markers of kidney damage, so supporting the renal protective effects of CD40 inhibition in lupus nephritis (55).

Moreover, anti-CD40 and anti-CD40L antibodies have shown promise for the treatment of lupus and lupus nephritis in clinical trials including human participants. A Phase II clinical trial evaluated the anti-CD40L antibody dapirolizumab pegol (CDP65) in patients with systemic lupus erythematosus (56). Specifically in those with active lupus nephritis, the results indicated that dapirolizumab pegol medication improved disease activity and renal function. This study indicated that treating lupus and preventing renal damage in affected individuals (57) could benefit from CD40-CD40L blockage as a successful therapy approach.

Moreover, studies of other anti-CD40 and anti-CD40L antibodies—including BI 655064 and iscalimab—have shown positive results in the treatment of autoimmune diseases, including lupus and lupus nephritis (58). In animal models and first clinical trials, these antibodies have shown the ability to reduce B cell activation, control T cell responses, and improve renal function. Importantly, these antibodies have been developed to lower the risk of thromboembolic events—a concern related to past generations of anti-CD40L antibodies (59).

The Potential of CD40-CD40L Inhibition in Systemic Lupus Erythematosus and Lupus Nephritis

Research by Shock et al., Perper et al., and others has demonstrated substantial evidence that targeting the CD40-CD40L pathway has considerable therapeutic advantages in the management of SLE and lupus nephritis (60). Inhibition of CD40-CD40L diminishes disease activity, enhances renal outcomes, and facilitates targeted immune modulation, rendering it a compelling choice for the management of these intricate autoimmune disorders (61). This therapy approach's primary advantage is its capacity to mitigate pathogenic immune responses responsible for lupus nephritis while preserving normal immunological function (62).

Moreover, the favorable outcomes from preclinical investigations have been corroborated by initial-phase clinical trials, indicating that CD40-CD40L blockage may serve as an effective and safe therapeutic option for patients with active lupus nephritis (63). The ongoing advancement of second-generation anti-CD40 and anti-CD40L antibodies, including BI 655064 and iscalimab, offers the potential for enhancing the safety and efficacy of CD40-CD40L-targeted treatments in systemic lupus erythematosus and lupus nephritis (64).

As our understanding of CD40-CD40L signaling in autoimmune diseases advances, CD40-CD40L blockade is likely to become a crucial part of the therapeutic options for treating SLE and lupus nephritis, thereby providing patients with a promising new strategy for managing these complex and debilitating disorders (65). Ongoing clinical studies and the development of increasingly advanced therapeutics suggest that CD40-CD40L blockage may greatly improve outcomes and quality of life for lupus nephritis patients (66). After proteinuria starts, which is a sign of lupus nephritis, patients received one dose of pegylated anti-CD40L monoclonal antibody (CDP654). Indeed, half of the treated patients showed disease remission, which demonstrates how well CD40L inhibition works as a therapeutic intervention in developed lupus nephritis (68). This drug helped to calm down T cells, reduced the production of interferon-I (IFN-I), and lowered the levels of inflammatory substances in the kidneys. The findings indicated that CD40L inhibition may control the immune system to reduce the inflammatory response responsible for kidney damage in lupus nephritis, so offering a possible course of treatment for patients with present disease (70).

Perper et al. (2017) conducted a comparable study examining the effects of a chimeric anti-CD40 monoclonal antibody (201A3) in NZB/W-F1 mice, which also develop lupuss (55). Therapy with 201A3 reportedly significantly reduced splenic germinal center development, T follicular helper (Tfh) cell counts, and proteinuria (71). This treatment restored glomerular architecture necessary for maintaining normal kidney function and greatly reduced immune cell invasion in the kidneys (72). The results were significant because they demonstrated that CD40 blockage could specifically focus on the immune

processes causing kidney damage in lupus, without the wide-ranging immune suppression that comes with other drugs like corticosteroids.

Rush et al. (2014) also validated these results by looking at anti-CD40 therapy in NZB/W-F1 mice showing lupus nephritis (74). Relative to control mice, anti-CD40 therapy was seen to reduce proteinuria, lower autoantibody synthesis, and increase survival. Importantly, anti-CD40 therapy lowered signs of kidney damage in tissue samples, giving more proof that blocking CD40-CD40L could help treat lupus nephritis. The study revealed that the therapeutic advantages of CD40 blocking could be sustained, indicating that CD40 inhibition could promote lifelong tolerance to inflammatory mechanisms in lupus (75).

These preclinical studies taken together provide a strong case for focusing on the CD40-CD40L pathway in lupus nephritis and systemic lupus erythematosus. The results of these studies consistently show that blocking CD40-CD40L can significantly help reduce disease activity and protect kidney function.

Clinical Trials and Mechanistic Insights

In reaction to early research findings, clinical trials have looked into how well blocking CD40-CD40L works in people with lupus nephritis and systemic lupus erythematosus (3, 77). In a clinical trial testing dapirolizumab pegol (CDP7657), an anti-CD40L antibody, in patients with SLE, good results were seen. Especially in patients with active lupus nephritis, this study revealed that dapirolizumab pegol dramatically increases renal function and disease activity. Strong data from the Phase II trial (78) suggests that targeting CD40-CD40L interactions may be a successful therapeutic approach for lupus and prevention of renal impairment in affected patients.

Second-generation anti-CD40 and anti-CD40L antibodies such as iscalimab and BI 655064 which have shown great promise in the treatment of autoimmune diseases, including lupus (79), have drawn more attention in further studies. Targeting CD40, a type of human-made antibody called BI 655064, blocks the interaction between CD40 and CD40L without causing platelet activation or producing cytokines. Both single and multiple ascending doses of BI 655064 produced over 90% occupancy of the CD40 receptor in healthy adults without generating thromboembolic events and prevented CD54 upregulation, a sign of B-cell activation. Phase II clinical studies in lupus nephritis patients are now in progress to confirm the efficacy of BI 655064 in humans. Preliminary data point to significant clinical benefits, including lower proteinuria and improved renal function, as well as a favorable safety record (58).

In a similar vein, preclinical models have shown that calimab (CFZ533), the Fc-silent, non-depleting anti-CD40 monoclonal antibody, efficiently reduces CD40 signaling (81). In studies with cynomolgus monkeys, iscalimab completely stopped the development of germinal centers and improved transplant survival without causing blood clotting issues. In a first-in-human trial, iscalimab was well tolerated; safety parameters showed no clinically significant changes (64). Currently undergoing a Phase II trial in patients with proliferative lupus nephritis, iscalimab's early data show notable therapeutic advantages in lowering disease activity and preserving renal function (82).

Focusing on the CD40-CD40L pathway in patients with lupus nephritis could strengthen the potential benefits seen in clinical trials for other autoimmune diseases, like rheumatoid arthritis and Sjögren's syndrome. Additionally, in a study with VIB4920, a specific protein targeting CD40L, patients with rheumatoid arthritis and healthy volunteers did not show any signs of platelet activation or clumping (83). These results suggest that blocking the CD40-CD40L pathway can control B-cell activity and lessen autoimmune diseases without causing harmful side effects (84).

A Phase IIa study of iscalimab in patients with primary Sjögren's syndrome showed it was effective, as patients had lasting responses for up to 32 weeks and lower scores on the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI). The study linked the therapeutic impact to decreases in the B-cell chemoattractant CXCL13 and a tendency for reduced levels of anti-SSA and anti-SSB autoantibodies. The fact that autoantibody levels did not change much when compared to RA patients shows how complicated autoimmune diseases are and that blocking CD40-CD40L can have different effects depending on the specific disease situation (85).

The main emphasis of the translation of preclinical results into human clinical trials has been anti-CD40 and anti-CD40L antibody evaluations in SLE and LN patients. Even though the first type of anti-CD40L antibodies, like ruplizumab (BG9588), caused safety problems, especially with blood clots, newer versions of these drugs have been created to lower these risks (86).

Originally tested in SLE patients in a Phase II trial, BG9588 is an anti-CD40L monoclonal antibody. Ruplizumab treatment lowered protein levels in urine, reduced autoantibody levels, and improved SLE Disease Activity Index (SLEDAI) scores in people with lupus nephritis, indicating that the disease might be managed effectively. Some patients experienced thromboembolic complications with other first-generation anti-CD40L antibodies a safety concern that calls for early trial termination (87).

Early Phase I trials found that BI 655064 achieved over 90% CD40 receptor occupancy in healthy volunteers without inducing thromboembolic

events. Phase II studies evaluating lupus nephritis patients have found BI 6550 to be an induction and maintenance treatment. Preliminary data shows a favorable safety record (88, 89) together with some obvious clinical benefits, including reduced proteinuria and enhanced renal function. Preclinical models using the Fc-silent anti-CD40 monoclonal antibody iscalimab (CFZ533) have shown a strong decrease in CD40-CD40L interactions. Iscalimab was well tolerated, showed no thromboembolic events, and decreased B-cell activation and germinal center development in a Phase I trial comprising healthy volunteers. The effectiveness of iscalimab in treating proliferative lupus nephritis is currently undergoing a Phase II trial (90).

A Phase I trial including SLE patients tested dapirolizumab pegol (CDP765), an anti-CD40L antibody fragment, with encouraging outcomes, including improved disease activity and a favorable safety profile free of thromboembolic events. Although it did not achieve its primary endpoint, a subsequent Phase IIb study demonstrated significant pharmacodynamic effects, including reductions in anti-dsDNA levels and proteinuria, indicating its potential as an alternative therapy for active SLE (56, 91).

These results indicate that blocking CD40 and CD40L could be a potential treatment for lupus nephritis and SLE. Whereas first-generation anti-CD40L antibodies faced safety concerns (92), second-generation agents, including BI 655064, iscalimab, and dapirolizumab pegol, show improved safety profiles and promising therapeutic effects; thus, they are strong candidates for further clinical development. The success of these drugs in reducing disease symptoms and protecting kidney function highlights the importance of blocking CD40-CD40L in treating lupus nephritis and other autoimmune diseases.

Conclusion

One intriguing course of treatment for SLE and LN is blocking the CD40-CD40L pathway. Early-stage clinical trials and preclinical research show tremendous therapeutic promise for lowering renal inflammation, autoantibody levels, and proteinuria—all hallmarks of these diseases. By addressing safety concerns related to thromboembolic events observed in previous therapies, second-generation anti-CD40 and anti-CD40L antibodies such as BI 655064, Iscalimab, and Dapirolizumab pegol offer hope for safer and more effective treatments. More recently developed drugs also target more precisely and lower unintentional immune activation. The outcomes of continuing Phase II studies will mostly define the safety and efficacy of these treatments in patients with SLE and LN. By focusing on reducing kidney damage, managing the disease better, and improving overall patient health, these drugs could significantly enhance the treatment of SLE and LN. Should these treatments be successful, they could be rather important for lupus management since they give patients more alternatives for treatment and reduce the long-term consequences of these autoimmune diseases. Blocking the CD40-CD40L pathway is one intriguing course of treatment for SLE and LN. In reducing renal inflammation, autoantibody levels, and proteinuria—all features of these diseases—early-stage clinical studies and preclinical research have shown tremendous therapeutic promise. Second-generation anti-CD40 and anti-CD40L antibodies, including BI 655064, Iscalimab, and Dapirolizumab pegol, give hope for safer and more effective treatments by addressing safety issues related to thromboembolic events seen in past therapies. More modern drugs also help reduce inadvertent immune activation and target it more precisely. The results of continuing Phase II studies will essentially define the safety and effectiveness of these treatments in patients with SLE and LN. If these treatments work well, they could be very important for managing lupus because they would provide patients with more treatment options and lessen the long-term effects of these autoimmune diseases. Should these treatments be successful, they could be rather important for lupus management since they give patients more choices for treatment and reduce the long-term consequences of these autoimmune diseases.

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