Novel Approved Targeted Therapies

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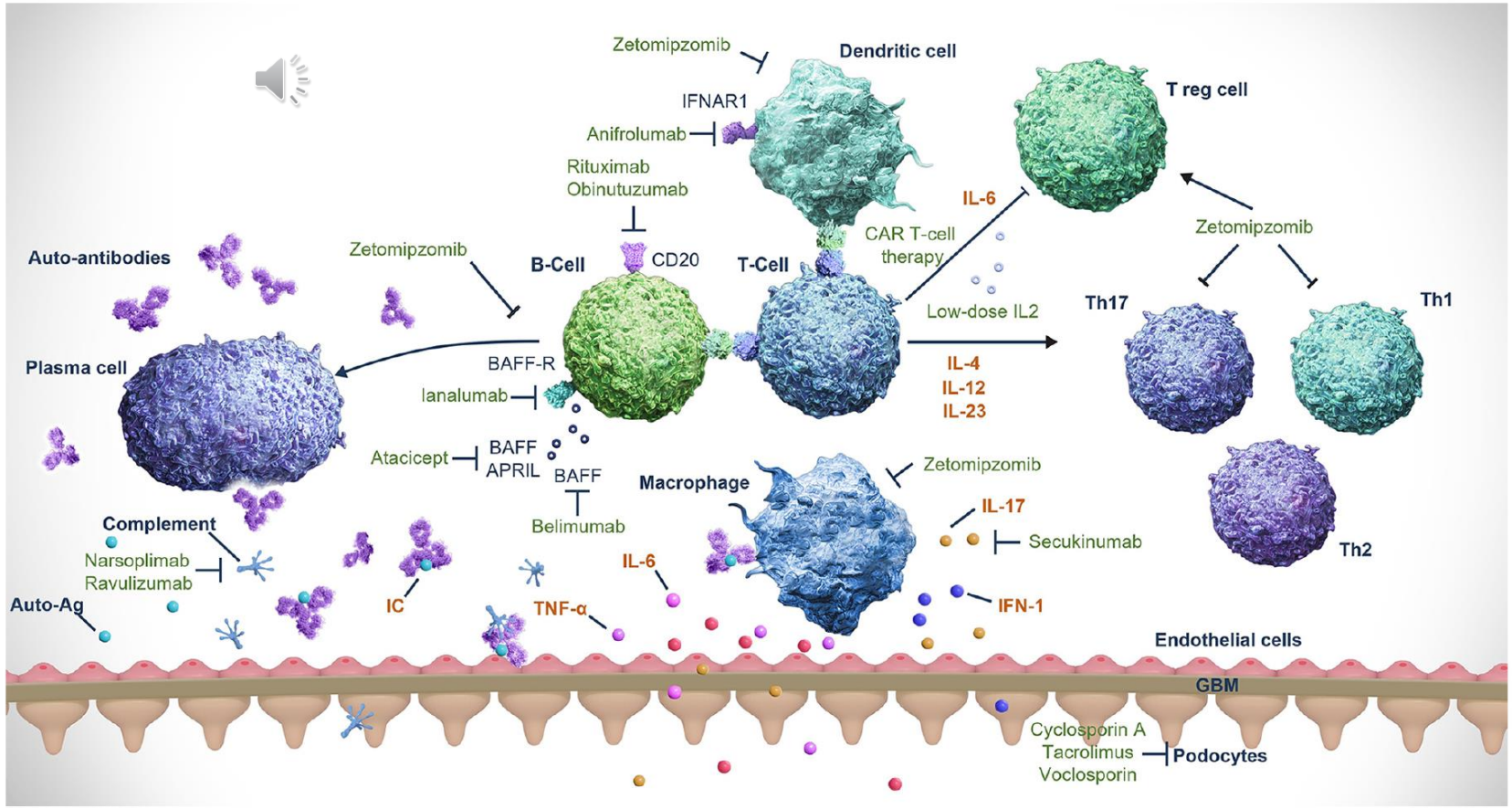
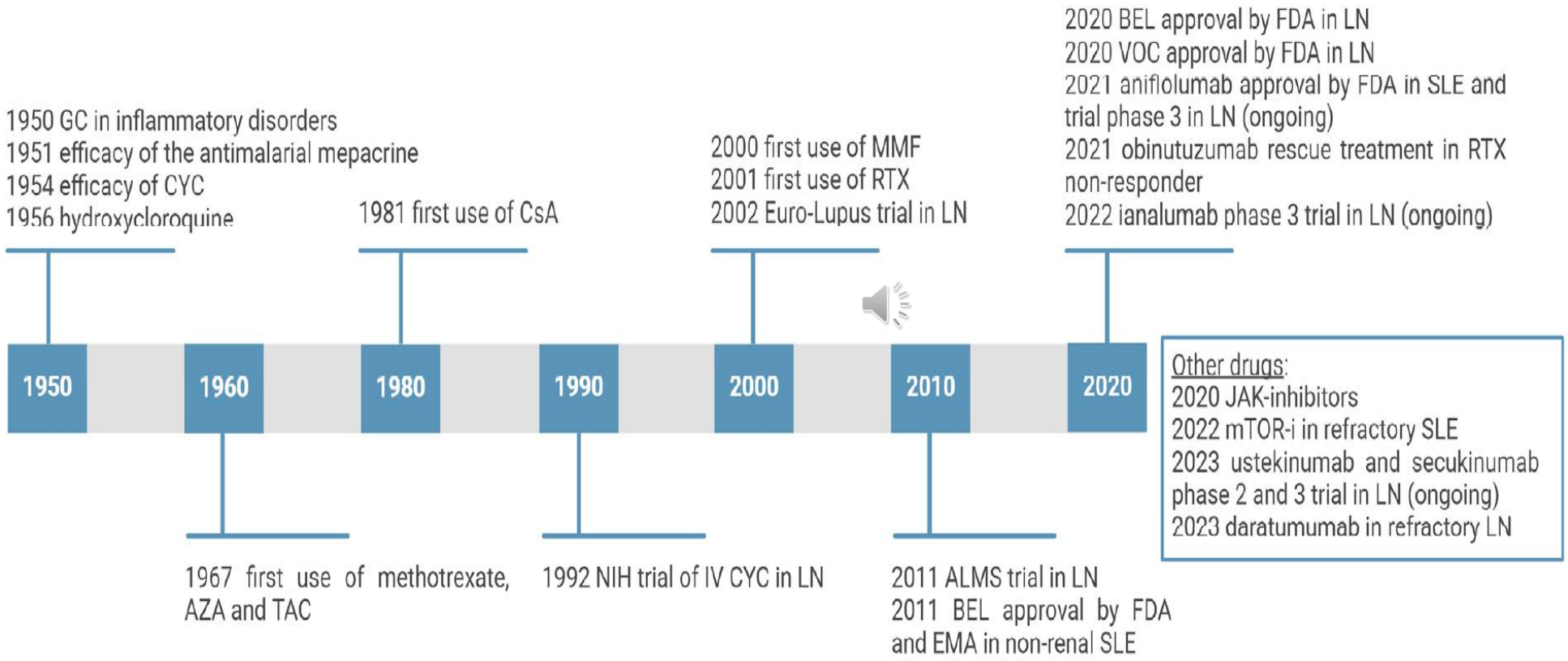


FIGURE 1

Mechanisms of action of treatments for LN. Ag, antigen; APRIL, a proliferation-inducing ligand (also known as ANP32B); ANP32B, acidic nuclear phosphoprotein 32 family member B; BAFF, B-cell activating factor (also known as TNFSF13B); BAFFR, B-cell activating factor receptor (also known as TNFRSF13C); CAR, chimeric antigen receptor; GBM, glomerular basement membrane; IFN, interferon; IFNAR1, interferon alfa and beta receptor subunit 1; IL, interleukin; LN, lupus nephritis; Th, T helper; TNF, tumor necrosis factor; TNFRSF13C, TNF receptor superfamily member 13C; TNFSF13B, TNF superfamily member 13B; T-reg cell, regulatory T-cell. Reprinted from Obrișcă B, et al. (50). Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/).

Therapeutic advances in SLE



01

Belimumab Overview

Mechanism of Action

01

Role of B Cells in SLE

B cells are crucial in the pathogenesis of systemic lupus erythematosus (SLE), primarily through the production of autoantibodies. They also enhance T-cell activation via antigen presentation, leading to increased inflammatory cytokine production, which contributes to the disease

02

Belimumab's Inhibition of BAFF

Belimumab targets the soluble form of B-cell activating factor (BAFF), a key protein that promotes B-cell survival and differentiation. By inhibiting BAFF, belimumab effectively reduces the number of mature B cells, thereby limiting pathogenic autoantibody production.

03

Impact on B-cell Survival

The inhibition of BAFF leads to a decrease in B-cell viability, which is fundamental in treating SLE. This reduction helps stabilize the immune system and prevent the exacerbation of autoimmune responses associated with the disease.

Clinical Trials

01

Phase III BLISS-LN Trial Results

The BLISS-LN trial demonstrated that patients receiving belimumab alongside standard therapy experienced a renal response rate of 43%, significantly higher than the 32% observed in the placebo group, indicating enhanced efficacy of the belimumab treatment.

02

Comparison with Placebo

In the trial, belimumab resulted in not only a higher renal response rate but also a markedly reduced risk of kidney-related events or death, showcasing its robust therapeutic potential compared to placebo.

03

Long-term Safety and Efficacy

Long-term data indicate that belimumab maintains a favorable safety profile, showing no increased incidence of adverse effects over a treatment period extending up to 11 years, reassuring its use in chronic conditions like lupus nephritis.

02

Voclosporin Overview

Mechanism of Action

Role of Calcineurin Inhibitors

Calcineurin inhibitors, including voclosporin, modulate T-cell activity by limiting lymphocyte proliferation and T-cell-mediated immune responses. This action is crucial in controlling autoimmune conditions, particularly in renal manifestations of SLE.

Advantages over Conventional CNIs

Voclosporin presents higher potency and a more stable pharmacokinetic profile compared to traditional CNIs like tacrolimus and cyclosporine, eliminating the need for rigorous therapeutic drug monitoring, thereby simplifying treatment regimens for patients.

Clinical Trials

Phase II AURA-LV Trial Findings

The AURA-LV trial highlighted that both low-dose and high-dose voclosporin produced significantly higher rates of complete renal remission compared to placebo. This underscores voclosporin's effectiveness in initiating treatment for lupus nephritis.

Phase III AURORA 1 Trial Results

The AURORA 1 trial reinforced the efficacy of voclosporin, showing a substantial improvement in complete renal response rates at 52 weeks compared to placebo, thereby solidifying its role in lupus nephritis treatment protocols.

Pooled Analysis of AURORA Studies

A pooled analysis from AURA-LV and AURORA 1 confirmed that voclosporin treatment led to higher rates of renal response, further establishing its importance as a frontline therapy for lupus nephritis.

03

Comparison of Therapies

Efficacy of Belimumab vs. Voclosporin

Renal Response Rates

Both belimumab and voclosporin demonstrate significant renal response rates; however, voclosporin offers advantages in certain patient demographics, suggesting differing effects in managing lupus nephritis.

Adverse Events and Safety Profiles

While both therapies exhibit relatively comparable safety profiles, initial observations indicated higher rates of serious adverse events with voclosporin, necessitating careful monitoring and patient-provider communication during treatment.

Recommendations from Guidelines

KDIGO 2024 Guidelines

The KDIGO 2024 guidelines recommend incorporating both belimumab and voclosporin as initial treatment options for lupus nephritis, highlighting their evidence-based effectiveness in clinical practice.

Updated EULAR 2023 Guidelines

The EULAR 2023 guidelines also advocate for the use of belimumab and voclosporin as key components in the treatment regimen for lupus, emphasizing the importance of tailored therapeutic strategies in diverse patient populations.

Rituximab Overview

Mechanism of Action

Rituximab works by targeting the CD20 protein on B cells, leading to their destruction through mechanisms such as complement-dependent cytotoxicity. This action is particularly useful in diseases involving excessive B-cell activity, including SLE.

Mixed Efficacy Data

Clinical studies of rituximab in treating SLE and lupus nephritis have produced inconsistent results, indicating a variable response and suggesting that while it can benefit some patients, its overall efficacy is uncertain.

Clinical Trial Insights

Phase III LUNAR Trial Results

The LUNAR trial noted that adding rituximab to standard therapy did not yield significant improvements in renal outcomes, suggesting limited utility of rituximab in routine treatment for lupus nephritis when used alone.

Post Hoc Analysis Findings

Post hoc findings from the LUNAR trial showed that patients achieving complete B-cell depletion had improved responses, indicating that effective B-cell targeting could enhance treatment outcomes, even amidst initial mixed results.

Targeted Therapies Under Investigation

Overview of B-cell Therapies

Importance of B-cell targeting

Targeting B-cells plays a crucial role in the treatment of autoimmune diseases such as lupus and Sjögren's syndrome, as B-cells are responsible for producing autoantibodies. Effective B-cell depletion can lead to significant clinical improvements, reducing disease activity and preventing organ damage.

Mechanisms of action

B-cell therapies, such as monoclonal antibodies, work by specifically binding to B-cell surface markers (e.g., CD20) or modulating key signaling pathways. This targeted approach facilitates B-cell depletion or modulation, reducing the inappropriate immune response characteristic of autoimmune diseases.

Clinical significance

The clinical significance of B-cell targeted therapies is underscored by their ability to improve patient outcomes, including faster remission rates, decreased disease flares, and enhanced overall quality of life. These therapies offer more precise treatments with potentially fewer side effects compared to traditional systemic therapies.

02

Obinutuzumab

Mechanism of Action

CD20 targeting

Obinutuzumab is a humanized monoclonal antibody that targets CD20, a protein expressed on B-cells. By binding to CD20, it mediates B-cell depletion through mechanisms such as antibody-dependent cellular cytotoxicity (ADCC), effectively reducing B-cell populations in patients.

Comparison with Rituximab

Compared to rituximab, obinutuzumab exhibits superior ADCC activity and greater efficacy in depleting resistant B-cell subpopulations. This differentiation positions obinutuzumab as a promising alternative for patients who may not respond adequately to standard B-cell-targeting therapies.

Enhanced ADCC and B-cell depletion

Enhanced ADCC by obinutuzumab leads to more effective B-cell depletion. In vitro studies demonstrate that obinutuzumab achieves substantial depletion rates in memory B-cells and plasmablasts, which are often resistant to conventional therapies, thereby improving overall treatment response.

Clinical Trials

01

Phase II NOBILITY trial results

The Phase II NOBILITY trial evaluated the efficacy of obinutuzumab in patients with lupus nephritis. The trial results indicated a higher proportion of patients achieving complete renal response at week 104 compared to placebo, highlighting its potential in improving renal outcomes.

02

Renal response outcomes

Renal response outcomes from the NOBILITY trial showed that 41% of patients receiving obinutuzumab achieved complete renal response at week 104. This substantial improvement suggests that obinutuzumab may offer significant benefits in managing renal manifestations of lupus.

03

Comparison of B-cell depletion rates

In the NOBILITY trial, 98% of patients in the obinutuzumab group achieved B-cell depletion within two weeks post-infusion. This contrasts sharply with lower depletion rates observed with rituximab, emphasizing obinutuzumab's higher efficacy in achieving sustained B-cell depletion.

Future Studies

01

Ongoing Phase III trials

The effectiveness of obinutuzumab is currently being evaluated in ongoing Phase III trials. These trials will provide further evidence of its therapeutic potential and help determine optimal treatment protocols in diverse patient populations.

02

REGENCY study overview

The global REGENCY study aims to assess the efficacy of obinutuzumab across a broader demographic, providing insights into its applicability and effectiveness in different geographical and genetic backgrounds. Results from this study will contribute to a better understanding of treatment variability.

03

Glucocorticoid-free management implications

Ongoing studies will explore obinutuzumab as a potential glucocorticoid-free treatment option during the induction phase of lupus nephritis management. The findings may reshape treatment guidelines and enhance patient safety by minimizing glucocorticoid-associated side effects.

03

Atacicept

Overview of Atacicept

Mechanism of action

Atacicept functions as a fully human recombinant fusion protein that inhibits both soluble and membrane-bound BAFF, as well as APRIL. This inhibition contributes to reduced B-cell and plasma cell levels, ultimately leading to a decrease in immunoglobulin production.

01

Targeting BAFF and APRIL

By targeting BAFF and APRIL, atacicept plays a critical role in modulating B-cell survival and proliferation. This dual targeting approach is significant for diseases characterized by B-cell dysregulation, offering a novel strategy to manage excessive B-cell activity.

02

Effects on B-cell and plasma cell levels

Atacicept significantly reduces the number of circulating B-cells and plasma cells, leading to lower serum levels of immunoglobulins such as IgG, IgM, and IgA. This reduction is crucial for controlling autoimmune responses in conditions like lupus and IgA nephropathy.

03

Clinical Findings

APRIL-LN trial and its termination

The Phase II/III APRIL-LN trial was designed to evaluate the efficacy of atacicept in lupus nephritis patients. However, it faced premature termination due to unexpected declines in serum IgG levels and serious infections, raising concerns about its safety profile.

JANUS study findings in IgA nephropathy

In the Phase II JANUS study involving IgA nephropathy, atacicept demonstrated a promising safety profile, significant proteinuria reduction, and stabilization of kidney function, indicating its potential therapeutic benefit outside of traditional lupus frameworks.

Current Status

COMPASS trial suspension

The COMPASS trial, initiated to further investigate atacicept's efficacy in lupus nephritis, was suspended as of July 2023. Despite this suspension, it was not attributed to safety concerns, suggesting that further evaluation may still be feasible.

Potential for future research

Future research on atacicept may focus on understanding its mechanisms better and identifying patient populations that could derive greater benefit. Ongoing studies will be crucial in determining the long-term safety and effectiveness of this therapy.

04

Ianalumab

Mechanism of Action

01

Dual targeting approach

Ianalumab utilizes a dual targeting approach to modulate B-cell survival, employing both direct lysis through ADCC and blockade of the BAFF receptor. This innovative mechanism aims to disrupt the dysregulated survival pathways that lead to B-cell persistence in autoimmune conditions.

02

BAFF receptor blockade

The blockade of BAFF receptors by ianalumab interrupts critical signaling pathways responsible for B-cell maturation and proliferation. This interruption results in enhanced B-cell depletion and offers a strategic method for controlling autoimmune flare-ups in susceptible patients.

03

Impact on B-cell survival

By effectively depleting B-cells and inhibiting their survival signals, ianalumab has demonstrated potential in reducing disease activity in autoimmune disorders. This dual mechanism addresses the root of B-cell dysregulation, paving the way for improved clinical outcomes in patients.

Clinical Trials

Phase II trial in Sjögren’ s syndrome

In a Phase II trial involving patients with primary Sjögren’s syndrome, ianalumab exhibited a significant dose-response relationship, which resulted in notable reductions in disease activity. This response highlights its potential applicability in conditions heavily characterized by B-cell involvement.

Comparison with other mAbs

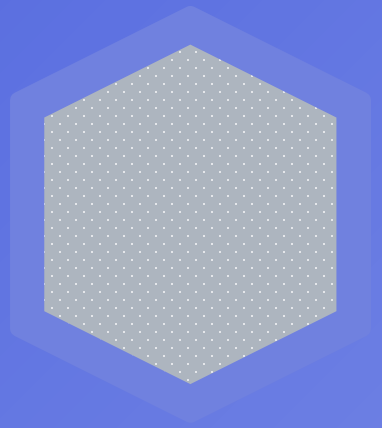
Unlike other monoclonal antibodies such as rituximab and belimumab, ianalumab demonstrated a more favorable efficacy profile in Sjögren’s syndrome. Its dual-targeting mechanism effectively addressed elevated BAFF levels, which are often a barrier to treatment with existing therapies.

05

Comparative Analysis of B-cell Therapies

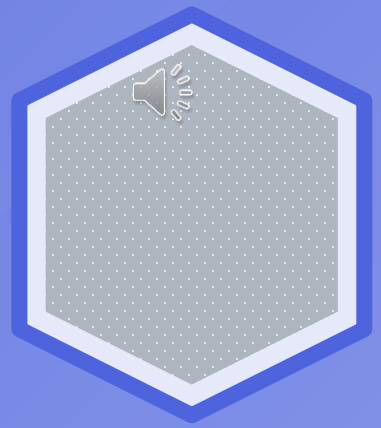
Efficacy Comparison

Obinutuzumab vs. Rituximab



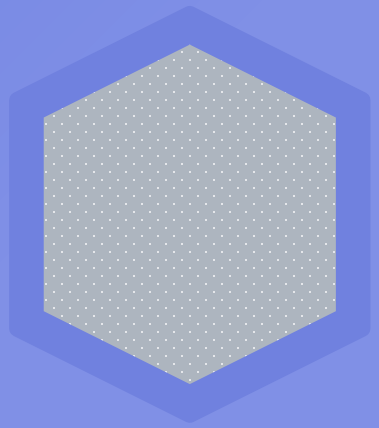
When comparing obinutuzumab to rituximab, obinutuzumab exhibits superior efficacy in achieving complete renal responses and sustained B-cell depletion, establishing itself as a compelling option for patients with difficult-to-treat lupus manifestations.

Atacicept effectiveness



Atacicept has demonstrated promising results in clinical trials, particularly in reducing proteinuria and stabilizing kidney function in IgA nephropathy and lupus nephritis. These findings indicate its potential to play a significant role in managing renal complications associated with autoimmune diseases.

Ianalumab results



Initial results from ianalumab trials suggest a favorable response in B-cell depletion and disease activity reduction, positioning it as a strong candidate for treating autoimmune disorders. Continued exploration into its therapeutic effects will be essential for confirming its place in the treatment landscape.

Therapies Targeting Cytokines in SLE and LN

Overview of Cytokines in SLE and LN

01

Role of IL-23/IL-17 Axis

The IL-23/IL-17 axis plays a pivotal role in the pathogenesis of Systemic Lupus Erythematosus (SLE) and Lupus Nephritis (LN), mediating vascular inflammation, leukocyte recruitment, and activation of B-cells, which leads to the production of autoantibodies.

02

Importance of Th17 Cells

CD4+ T-helper cells, specifically Th17 cells that secrete IL-17, are critical in exacerbating kidney inflammation and tissue damage in patients with SLE and LN, reinforcing the significance of targeting these pathways in therapeutic strategies.

03

Association with Disease Prognosis

Elevated levels of IL-17 are found in LN patients, which correlate with worse clinical outcomes, highlighting the importance of this cytokine as a biomarker for disease severity and prognosis.

Current Cytokine Targeting Approaches

General Strategies

Current therapies focus on inhibiting specific cytokines, such as IL-17 and Type I interferons, to modulate immunological responses in SLE and LN, thereby potentially reducing kidney damage and improving patient outcomes.

Importance of Personalized Therapy

Tailoring treatment strategies to individual patient profiles, including cytokine levels and disease severity, is crucial for enhancing efficacy and minimizing adverse effects of treatments.

02

Secukinumab

Mechanism of Action

Anti–IL-17A Inhibition

Secukinumab is designed to specifically inhibit IL-17A, a cytokine implicated in promoting inflammation and immune responses associated with SLE, thereby preventing its interaction with IL-17 receptors on various cells.

Blocking Cytokine Interaction

By blocking the IL-17A interaction, secukinumab reduces pro-inflammatory signaling pathways that contribute to tissue damage and autoimmune responses in SLE and LN.

Clinical Evidence

01

Future Directions in Research

Future research will focus on elucidating the effects of secukinumab on renal endpoints and overall disease activity in SLE patients, paving the way for potential regulatory approvals.

02

Case Reports Overview

Limited case reports have illustrated the potential benefit of secukinumab in treating refractory cases of LN, indicating a need for further large-scale clinical investigations to validate these observations.

03

Ongoing Clinical Trials

The SELUNE Phase III clinical trial (NCT04181762) and the ORCHID-LN Phase II trial (NCT04376827) are underway, aiming to clarify the therapeutic potential of secukinumab and other IL-23 inhibitors in managing LN.

03

Anifrolumab

Mechanism of Action

Type I Interferon Role in SLE

Type I interferons are central to the pathophysiology of SLE, as they are involved in promoting inflammation, immune dysregulation, and kidney damage through activation of immune complexes and leukocyte recruitment.

Inhibition of IFN Signaling

Anifrolumab is a monoclonal antibody that specifically targets the type I IFN receptor, effectively blocking IFN signaling pathways and reducing the pathological effects associated with chronic inflammation in SLE and LN.

Clinical Trial Insights

01

Phase III TULIP-2 Trial Results

The Phase III TULIP-2 trial demonstrated a significant reduction in disease activity in nonrenal SLE patients treated with anifrolumab compared to placebo, although LN patients were not included.

02

Phase II TULIP-LN Trial Overview

In the Phase II TULIP-LN trial, patients with LN were randomized to receive anifrolumab in different regimens combined with standard treatments, but the primary endpoint was not met, indicating challenges in treatment efficacy.

03

Statistical Analysis of Results

The statistical analysis from the trial indicated no significant differences in renal response rates or changes in proteinuria between treatment arms, suggesting the need for alternative dosing strategies.

Challenges and Considerations

01

Suboptimal Drug Exposure

Anifrolumab's reduced therapeutic efficacy in LN may be attributed to suboptimal drug exposure with standard dosing regimens, highlighting the need for optimized administration protocols for this specific patient population.

02

Impact of Proteinuria

Proteinuria in LN patients may lead to increased clearance rates of anifrolumab, further complicating the therapeutic approach and necessitating careful monitoring and adjusting of dosages in clinical settings.

03

Recommendations for Future Trials

Future clinical trials should focus on dosing regimens that ensure adequate serum levels of anifrolumab and consider the unique pharmacokinetic profiles of LN patients to improve treatment outcomes.

Phase III IRIS Trial

Objectives and Goals

The Phase III IRIS trial (NCT05138133) aims to investigate the efficacy and safety of anifrolumab specifically in LN patients, with goals to assess renal outcomes and overall disease activity.

Expected Outcomes

Expected outcomes include improvements in renal function, reductions in proteinuria, and a better understanding of the drug's impact on long-term patient prognosis and quality of life.

Comparative Analysis

Secukinumab vs. Anifrolumab

Comparison between secukinumab and anifrolumab will be critical to understanding their distinct mechanisms and efficacy in treating SLE and LN, focusing on cytokine pathway modulation.

IL-23 Inhibitors in Current Trials

The ongoing exploration of IL-23 inhibitors in various clinical trials represents a promising area in managing autoimmune disorders such as SLE and LN, potentially leading to more targeted therapeutic options.

01

Immunoproteasome Targeting Therapies

Zetomipzomib Overview

Role of Proteasomes

Proteasomes are fundamental to cellular regulation as they degrade intracellular proteins, helping maintain cellular homeostasis and controlling key signaling pathways. This process is vital for ensuring that cells can properly manage their internal environments and respond to external stimuli.

Immunoproteasomes in Immune Function

Immunoproteasomes are specialized proteasomes predominantly found in immune cells and play a significant role in immune processes, including the presentation of antigens, cytokine production, and the functioning of plasma cells. Their expression can increase in response to inflammatory conditions, enhancing immune responses.

Evidence from Murine Models

Studies in mouse models have demonstrated that selective inhibition of immunoproteasomes leads to significant immunomodulatory effects, including reducing proinflammatory cytokines and altering T cell differentiation, indicating their potential as a therapeutic target in inflammatory diseases like lupus nephritis.

Clinical Efficacy in Lupus Nephritis

01

Phase II Trial Results

In a Phase II trial involving patients with lupus nephritis, significant renal response rates were observed, with 64.7% achieving a reduction in urinary protein to creatinine ratio (UPCR) of over 50%, underscoring the therapeutic potential of zetomipzomib in managing this condition.

02

Patient Outcomes and Safety

Patient outcomes from clinical trials indicate that alongside the beneficial effects on renal function, zetomipzomib maintains a favorable safety profile, with no significant impact on the normal immune response, making it a promising candidate for treatment without the adverse effects associated with broader immunosuppression.

03

Ongoing Studies and Future Directions

Ongoing evaluations, such as the Phase IIb PALIZADE trial, seek to further assess the efficacy of zetomipzomib in active lupus nephritis, indicating a commitment to advancing this therapy through comprehensive clinical research.

CAR-T Therapy Introduction

Mechanism of Action

CAR-T therapy involves engineering T cells to target specific antigens on B cells, potentially leading to effective B cell depletion in patients with systemic lupus erythematosus (SLE) and lupus nephritis. This approach leverages the precision of cellular therapy to modulate the patient's immune response.

Clinical Experience in SLE & LN

Initial clinical experiences show promising results of CAR-T therapy in achieving significant B-cell depletion, which is critical for improving disease outcomes in refractory cases of SLE and lupus nephritis, pointing towards a novel therapeutic strategy.

Case Reports and Efficacy

Significant Patient Case

A notable case involved a 20-year-old woman with severe, treatment-resistant SLE and lupus nephritis who experienced marked improvement after receiving anti-CD19 CAR-T therapy, highlighting its potential efficacy in managing difficult cases.

Series of Patient Responses

Subsequent case series have corroborated the positive outcomes observed, demonstrating substantial reductions in disease activity and improvements in serological markers across multiple patients receiving anti-CD19 CAR-T therapy for refractory lupus nephritis.

Future Research Directions

Need for Larger Trials

There is a critical need for larger, well-designed randomized clinical trials to investigate the long-term efficacy and safety profiles of anti-CD19 CAR-T therapy in broader patient populations affected by lupus nephritis.

Current Clinical Studies

An open-label Phase I/II study is currently assessing YTB323, an anti-CD19 CAR-T therapy, for its safety and efficacy in refractory SLE and lupus nephritis, indicating an active pursuit of robust evidence to support this treatment modality.

03

Interleukin-2 Therapies

Role of IL-2 in Immune Regulation

Importance in Self-Tolerance

Interleukin-2 (IL-2) is crucial for maintaining T-cell mediated self-tolerance by promoting the survival and proliferation of regulatory T cells (Tregs), thus preventing autoimmune responses that are characteristic of conditions such as lupus.

Effects of Decreased IL-2

Reduced levels of IL-2 have been linked to decreased Treg populations and increased disease activity in lupus-prone models, highlighting the importance of adequate IL-2 production in the prevention of autoimmune manifestations.

Low-Dose IL-2 Trials

Patient Outcomes

In trials assessing low-dose IL-2 treatment in lupus patients, significant expansions in Treg populations were observed, resulting in remarkable drops in disease activity and improved clinical outcomes, suggesting therapeutic benefits.

Comparison with Placebo

A randomized clinical trial showed that patients receiving low-dose IL-2 had over three times the rate of complete remission compared to a placebo group, underscoring the potential effectiveness of this approach in treating lupus nephritis.

04

Complement-Targeting Therapies

Understanding Complement Activation

Role in Kidney Damage

Dysregulation of the complement system can lead to impaired clearance of immune complexes and debris, contributing to kidney damage in lupus nephritis, highlighting the need for targeted therapies that address these mechanisms.

Impact on SLE and LN

Abnormal complement activation has been implicated in the pathogenesis of lupus and its renal manifestations, emphasizing the importance of complement-targeting therapies as potential intervention strategies in these diseases.

Narsoplimab and Ravulizumab

Mechanisms of Action

Narsoplimab inhibits mannan-binding lectin-associated serine protease 2, affecting the lectin pathway of complement activation, while Ravulizumab acts as a terminal complement inhibitor by blocking the cleavage of complement protein C5, preventing harmful immune responses.

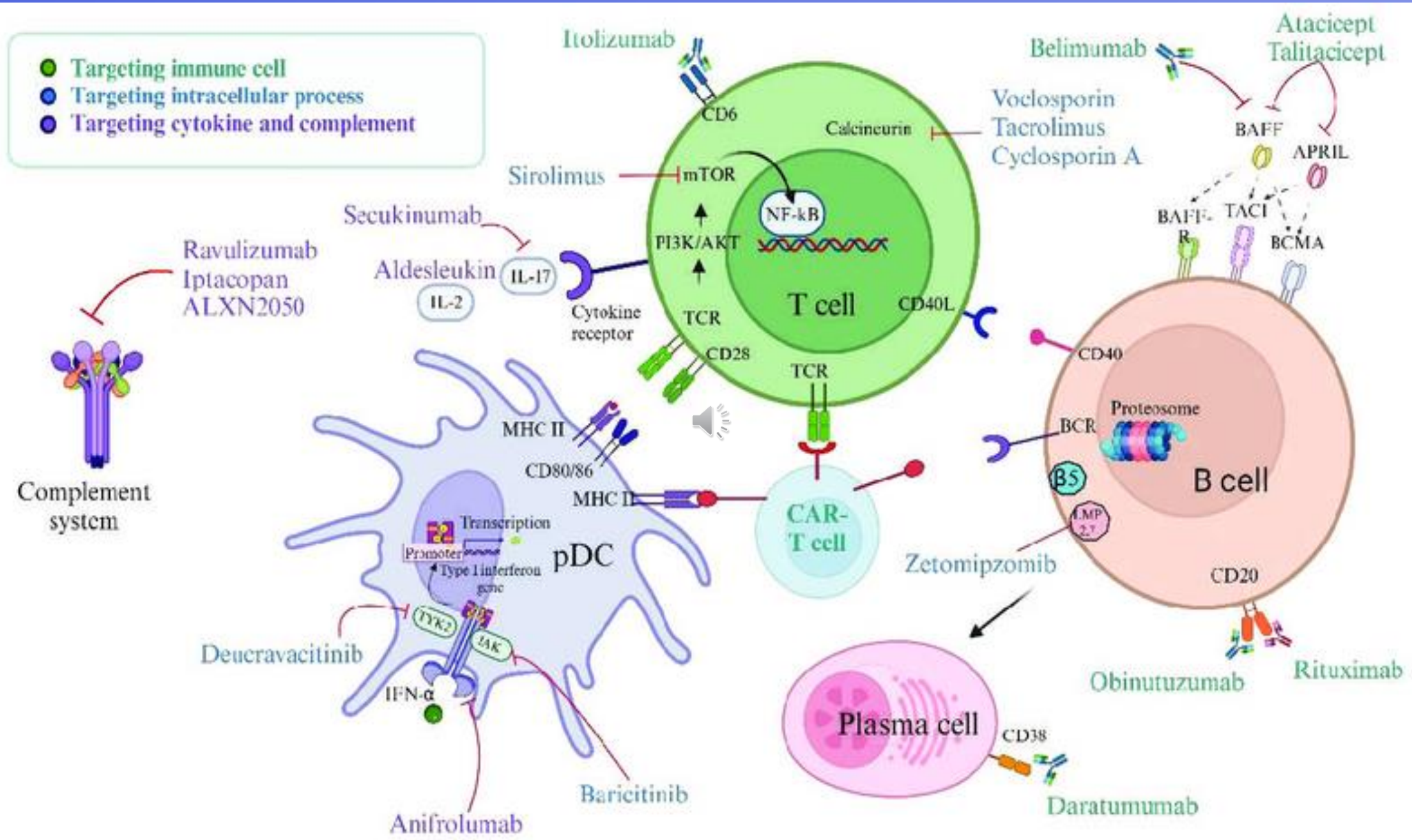
Current Clinical Trials

Both narsoplimab and ravulizumab are currently undergoing Phase II clinical trials for their efficacy in lupus nephritis, with ongoing efforts to establish their safety and therapeutic benefits in managing this complex condition.

TABLE 1 Summary of evidence for select novel treatments for LN.

Therapeutic agent	Mechanism of action	Trial	Patient population	Enrollment	Key results
Belimumab	BAFF (also known as TNFSF13B) inhibitor	BLISS-LN; Phase III (51)	Patients with active LN	448	Significantly improved renal response rates (OR: 1.6, 95% CI: 1.0–2.3; $p = 0.03$)
Voclosporin	Calcineurin inhibitor	AURORA 1; Phase III (52)	Patients with active LN	357	Significantly improved complete renal response rates (OR: 2.65; 95% CI: 1.64–4.27; $p < 0.0001$)
Rituximab	CD20-directed monoclonal antibody	LUNAR; Phase III (53)	Patients with active LN	72	Similar renal response rates as placebo ($p = 0.55$)
Obinutuzumab	CD20-directed monoclonal antibody	NOBILITY; Phase II (54)	Patients with active LN	125	Significantly improved complete renal response rates (difference: 19%; 95% CI: 2.7%–35%; $p = 0.026$) and overall renal response rates (difference: 25%; 95% CI: 8.2–42%; $p = 0.005$)
Atacicept	BAFF (also known as TNFSF13B) and APRIL (also known as ANP32B) inhibitor	APRIL-SLE; Phase II/III (55)	Patients with active SLE	246	Post hoc analysis: observed dose-response relationship between atacicept concentrations, reduced Ig levels, and reduced flare rates
Ianalumab	BAFFR (also known as TNFRSF13C) inhibitor	SIRIUS-LN; Phase III	Patients with active LN	≈420	Ongoing; estimated primary completion date: March 2027 (56)
Secukinumab	Anti-IL-17A inhibitor	SELUNE; Phase III	Patients with active LN	275	Ongoing; estimated study completion date: Jan. 2026 (57)
Anifrolumab	Type I IFN receptor inhibitor	TULIP-LN; Phase II (58)	Patients with active LN	147	Similar mean difference from baseline in 24-hour UPCR (GMR: 1.03; 95% CI: 0.62–1.71; $p = 0.905$; GMR <1 favors anifrolumab) and renal response (difference: −0.1%; 95% CI: −16.9% to 16.8%; $p = 0.993$)
Zetomipzomib	Immunoproteasome inhibitor	MISSION trial; Phase II (59)	Patients with active LN	17	64.7% of patients had ≥50% reduction in UPCR from baseline, and 35.3% achieved a complete renal response at week 25
YTB323	Anti-CD19 CAR-T therapy	Open-label Phase I/II	Patients with severe, refractory SLE	≈27	Ongoing; estimated completion date: October 2026 (60)
Low-dose IL-2	Promote T-reg cells	He et al.; Phase II (61)	Patients with active SLE	60; 25 of these had LN	In patients with LN: significantly improved complete remission rates (53.85% in IL-2 group vs. 16.67% in placebo group; $p = 0.036$)
Ravulizumab	Complement inhibitor	SANCTUARY; Phase II	Patients with active LN or IgAN	≈120	Ongoing; estimated primary completion date: April 2024 (62)
Narsoplimab	Complement inhibitor	Open-label Phase II (63)	Patients with LN ($n = 5$) and other nephropathies	≈54	Preliminary data: mean 69% reduction in 24-h urine protein excretion over the treatment period in 4 of 5 patients with LN (63)

ANP32B, acidic nuclear phosphoprotein 32 family member B; APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BAFFR, BAFF receptor; GMR, geometric mean ratio; IgAN, immunoglobulin A nephropathy; IL, interleukin; LN, lupus nephritis; OR, odds ratio; SLE, systemic lupus erythematosus; TNFRSF13C, TNF receptor superfamily member 13C; TNFSF13B, TNF superfamily member 13B; UPCR, urine protein creatinine ratio.


Targeting immune cell
Targeting intracellular process
Targeting cytokine and complement
Itolizumab
CD6
Calcineurin
Voclosporin
Tacrolimus
Cyclosporin A
Belimumab
Atacicept
Talitacicept
BAFF
APRIL
Sirolimus
mTOR
NF-kB
PI3K/AKT
T cell
Secukinumab
Aldesleukin
IL-17
IL-2
Cytokine receptor
TCR
CD28
CD40L
BAFF-R
TACI
BCMA
Ravulizumab
Iptacopan
ALXN2050
Complement system
CD40
Proteosome
BCR
B5
LMP 2,7
B cell
MHC II
CD80/86
MHC II
CAR-T cell
Transcription
Promoter
Type 1 interferon gene
pDC
Zetomipzomib
CD20
TYK2
JAK
Deucravacitinib
IFN-α
Plasma cell
CD38
Obinutuzumab
Rituximab
Baricitinib
Anifrolumab
Daratumumab