Mechanisms and New Strategies for Primary Sjögren's Syndrome

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Abstract

Primary Sjögren's syndrome (SS) is a common chronic autoimmune disease characterized by lymphocytic infiltration of exocrine glands, mainly salivary and lacrimal, resulting in oral and ocular dryness, although virtually any organ system can be affected. SS-related systemic manifestations are classified as either related to the presence of periepithelial infiltrates in exocrine and parenchymal organs or resulting from immunocomplex deposition due to B cell hyperactivity with increased risk for B cell lymphoma development. Activation of both innate and adaptive immune pathways contributes to disease pathogenesis, with prominent interferon (IFN) signatures identified in both peripheral blood and affected salivary gland tissues. Recently, LINE-1 genomic repeat elements have been proposed as potential triggers of type I IFN pathway activation in SS through activation of Toll-like receptor–dependent and –independent pathways. In view of the increasingly appreciated variability of SS, elucidation of distinct operating pathways in relation to diverse clinical phenotypes and selection of the optimal therapeutic intervention remain major challenges. Inhibition of cathepsin S molecules, blockade of costimulation through administration of abatacept and inhibitors of B7-related molecules and CD40, blockade of B cell function and B cell survival factors, and disruption of the formation of ectopic germinal centers are considered the main therapeutic targets. Well-controlled multicenter clinical trials are ongoing and data are awaited.

INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune disorder that typically presents with oral and ocular dryness as a result of mononuclear infiltration of the affected organs, chiefly salivary and lacrimal glands. Female preponderance, B cell hyperactivity expressed as hypergammaglobulinemia, and the presence of several serum autoantibodies, as well as activation of type I interferon (IFN) pathways, are disease hallmarks also shared by other systemic autoimmune disorders, implying common underlying pathogenic mechanisms (1, 2). SS is defined as primary when it presents alone and as secondary in association with other diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis (2).

Manifestations arising from organ involvement beyond the exocrine glands also occur quite commonly, affecting approximately half of primary SS patients. Depending on the underlying pathology, extraglandular features can be classified as either periepithelial (driven by lymphocytic infiltration around epithelial tissues of parenchymal organs such as lung, kidney, and liver) or mediated by deposition of immunocomplexes as a result of profound B cell reactivity such as purpura, glomerulonephritis, and peripheral neuropathy (3). Immunocomplex-mediated features, along with salivary gland enlargement, cryoglobulinemia, C4 hypocomplementemia, rheumatoid factor (RF) positivity, and monoclonal gammopathy, have been previously designated as adverse predictors for lymphoma development in the context of primary SS, denoting a high-risk, aggressive disease phenotype (3–7).

In recent years, the increasing recognition of the disease's heterogeneity, the availability of biologic agents, and the better elucidation of pathogenetic pathways have enhanced international efforts to conduct well-controlled studies in the setting of primary SS. In this review, we summarize the evidence on the major pathways involved in disease pathogenesis, as well as the developing therapeutic strategies. It should be emphasized that prompt identification of high-risk individuals, so as to initiate therapies aimed at decelerating or arresting progression to lymphoma, remains one of the main challenges in the current management of SS.

INNATE IMMUNITY COMPONENTS

Proinflammatory Cytokines

Proinflammatory cytokines including interleukin (IL)-1, tumor necrosis factor (TNF), and IL-6 have long been found to be upregulated in salivary gland tissues from patients with SS (8). However, administration of TNF blockers in primary SS patients not only failed to alleviate symptoms (9–11) but also led to a significant rise in gammaglobulins and serum IgM titers (9). These observations could be related to augmentation of the already activated type I IFN system in SS and subsequent increase of B cell activating factor (BAFF) (12).

IL-1 signaling on brain neurons has been previously postulated as a key event in the pathogenesis of sickness behavior, a condition resembling chronic fatigue, which frequently occurs in the setting of SS (13). In support of this hypothesis, IL-1 receptor antagonist (IL-1ra, Anakinra) given in the context of a double-blind placebo-controlled clinical trial resulted in a 50% reduction in fatigue in a higher percentage of patients on the active drug compared to placebo (14). It should be emphasized, however, that the primary endpoint of the study was not reached. Another cytokine of the IL-1 family shown to be raised in both serum and salivary gland biopsies of SS patients is IL-33, acting synergistically with IL-12 and IL-23 for the induction of IFNγ secretion by natural killer (NK) and NKT cells (15). NKT cells share features of both T and NK cells.

IL-6 levels were also found to be heightened in serum, saliva, and tears of patients with primary SS, and SS-derived salivary gland epithelial cells have been shown to produce IL-6, through which

they are able to activate T-follicular cells (16, 17). The contributory role of IL-6 in differentiation of Th1, extrafollicular T helper cells, germinal center B cells, and plasma cells in the spleen has been shown in a recent study of a murine lupus model associated with secondary SS. Following genetic IL-6 depletion, both lupus and SS-related features such as salivary gland infiltrations and autoantibody responses against La/SSB (La protein/Sjögren's syndrome antigen B) were abrogated (18), reinforcing the idea of administration of the IL-6 receptor antagonist tocilizumab in SS (ongoing phase II trial NCT01782235).

Interferons

A growing body of evidence derived from microarray and gene expression studies in both peripheral blood and minor salivary gland (MSG) tissues from SS patients revealed upregulation of genes induced by IFNs—type I (mainly IFNα and β), type II (IFNγ), or both—the so-called IFN signature (19–21). Whereas plasmacytoid dendritic cells are considered the main source of IFNα (22), Th1 CD4$^+$ helper cells and NK cells are viewed as the main IFNγ producers in SS salivary gland tissues (23, 24). In an attempt to clarify whether type I or II IFNs contribute to SS pathogenesis—taking into account disease heterogeneity (3), the significant overlap between the genes induced by types I and II (20), and the different types of samples used in different studies (19, 20)—both type I and II IFNs, as well as their inducible genes, were explored in both peripheral blood and MSG tissues from primary SS patients with well-characterized distinct clinical phenotypes. According to these findings, the type I IFN signature seemed to prevail in peripheral blood of SS patients, in contrast to the type II IFN signature, which is predominant in SS MSG biopsies. Additionally, the presence of low IFNα and high IFNγ transcript levels in MSG tissues was strongly associated with SS concomitant with lymphoma, and the IFNγ/α mRNA ratio in MSG diagnostic biopsies was proposed as a putative novel tissue biomarker in the diagnosis of salivary extranodal SS-related non-Hodgkin's lymphoma (25).

Identifying the primary triggers of type I IFN pathway activation in the setting of systemic autoimmunity remains a challenge. Recent findings indicate that overexpression of the normally silent endogenous virus-like genomic repeat element LINE-1 (long interspersed nuclear element–1) in salivary gland tissues from SS patients, which results from defective methylation, might induce activation of type I IFN pathways (26). Once produced, type I IFNs cause apoptosis of salivary epithelial cells, exposure of endogenous autoantigens to the immune system, upregulation of BAFF expression, increased B cell survival and differentiation, and ultimately autoantibody production and immunocomplex formation. The upstream events leading to demethylation, however, remain to be defined (1). Alu retroviral sequences have also been recently proposed as IFN inducers in the setting of autoimmunity through stimulation of Toll-like receptor pathways (27).

ACTIVATION OF ADAPTIVE IMMUNITY MECHANISMS

Antigen Presentation

It has been recently appreciated that cathepsin S—a major cysteine endoprotease located in the lysosomes of antigen-presenting cells—is involved in controlling autoantigen presentation to CD4$^+$ T cells or to NK1.1$^+$ T cells by interfering with the binding of MHC II or CD1 molecules, respectively (28). Additionally, cathepsin S has been recently proposed as a disease biomarker because of its heightened levels in tears of SS patients (29). In this context, cathepsin S inhibition in a murine SS model resulted in impaired presentation of the SS-related autoantigen alpha fodrin and reduction of autoantigen-specific T cell responses in vitro, as well as in decrease of lymphocytic

infiltration in salivary and lacrimal glands and autoantibody titers in vivo. Given the therapeutic potential of cathepsin S inhibition, a randomized trial in patients with primary SS is currently under way (**Table 1**, NCT02701985).

Costimulation

Costimulation has been viewed as a central event in the perpetuation and amplification of abnormal immune response in chronic inflammatory reactions, and administration of a blocking signal or inhibition of a stimulatory signal is considered crucial for the treatment of autoimmune diseases. The first type of costimulatory molecule recognized was the B7/B7 ligand family; B7 molecules expressed on classic antigen-presenting cells play a critical role in the regulation of immune responses by providing activation or inhibitory signals to T cells, through the ligation with CD28 or CTLA4 receptors, respectively. The second type of costimulatory molecule is the TNF/TNF receptor family (responsible for interactions of CD40 on B cells with CD154/CD40 ligand on T cells, endothelial and epithelial cells, B cells, or antigen-presenting cells). In primary SS, CD80, CD86, and CD40 molecules were found to be expressed on salivary gland epithelial cells, indicating an intrinsically activated phenotype, capable of orchestrating local immune responses (30).

These findings—together with encouraging therapeutic results in murine models of SS following administration of either an antibody against CD86 or a CD152-Ig fusion protein (31, 32), both of which prevent costimulation—prompted a trial of the humanized fusion protein CD152-IgG1 (abatacept) in primary SS. Administration of abatacept, already licensed for the treatment of rheumatoid arthritis, resulted in initial favorable responses in regard to glandular and systemic features, extent of lymphocytic infiltrates, and RF and IgG levels (33–35). Results from an ongoing randomized trial (NCT02067910) with abatacept are eagerly awaited before definite conclusions are drawn. Antibodies directed against B7-related molecules and CD40 are also under way (NCT02334306, NCT02291029) (**Table 1**).

B Cell Activation

B cell activation is a cardinal feature of SS manifested as hypergammaglobulinemia, germinal center formation at the site of salivary gland tissue, RF positivity, and raised autoantibody titers against ribonucleoprotein complexes (2). Although the drivers of B cell activation in the setting of SS remain unexplored, both genetic and environmental factors are increasingly recognized as potential contributors. Thus, on the one hand, data derived from both genome-wide association and case-control studies revealed a number of genes involved in B cell survival and signaling (reviewed in 36). On the other hand, the presence of germinal center–like structures and the local production of heavily somatically hypermutated autoantibodies in salivary glands imply the antigen-driven nature of the local immune response elicited at the level of salivary glands, although recent data supported the idea of antigen-independent activation through interaction with N-glycosylation motifs acquired during somatic hypermutation (37, 38). Abnormal retention of preswitch immunoglobulin transcripts in circulating memory B cells, prolonged translocation of B cell receptor (BCR) in lipid rafts of B cells resulting in increased signaling, and raised BAFF levels in serum, saliva, and salivary glands of patients have also been viewed as significant contributors (39). Recent evidence additionally suggests B cell activation in the setting of SS could be related to the absence—at the level of inflamed salivary gland tissues—of NKT cells (40), which have been shown to restrict the activity of autoreactive B cells prior to their entry in the germinal centers (41).

Table 1 Studies of agents influencing adaptive immune pathways

Pathway	Registration number	Medication	Type of study	Status
Antigen presentation				
Cathepsin-S inhibition	NCT02701985	RO5459072	Multicenter, randomized, double-blind, placebo-controlled, parallel-group phase IIa	Ongoing
Costimulation				
CD152-IgG1	NCT02067910	Abatacept	Randomized, double-blind, placebo-controlled phase III	Ongoing
B7-related protein inhibitor	NCT02334306	AMG 557/ MEDI5872	Phase IIa, multicenter, randomized, double-blind, placebo-controlled, parallel-group	Ongoing
Anti-CD40	NCT02291029	CFZ533	Multicenter, randomized, double-blind, placebo-controlled, parallel-group	Ongoing
B cell activation				
BAFF/BAFF-R axis				
BAFF blockade	NCT01008982	Belimumab	Phase II, proof-of-concept, 52-week open study	Completed (65)
BAFF-R modulation	NCT02149420	VAY736	Single-dose, double-blind, placebo-controlled	Ongoing
B cell/plasma depletion				
Anti-CD20	NA	Rituximab	Randomized, double-blind, placebo-controlled, pilot	Completed (42)
	ISRCTN65360827	Rituximab	Multicenter, randomized, parallel-group, double-blind, placebo-controlled trial (TRACTISS)	Preliminary results (51)
	NCT00363350	Rituximab	Phase II, double-blind, randomized, placebo-controlled trial	Completed (46)
	NCT00740948	Rituximab	Multicenter, randomized, double-blind, placebo-controlled trial (TEARS)	Completed (47)
Proteasome inhibitor	NA	Bortezomib	Limited data from case reports	NA
Combination of BLyS blockade and B cell depletion	NCT02631538	Belimumab and rituximab	Phase II, multinational, multicenter, double-blind (sponsor open), randomized, placebo-controlled	Ongoing
BCR signaling				
Anti-CD22	NA	Epratuzumab	Open-label, phase I/II	Completed (80)
PI3Kδ inhibitors	NCT02610543	UCB5857	Randomized, double-blind, placebo-controlled, proof-of-concept	Ongoing
Btk inhibitors	NA	NA	NA	NA
Germinal center formation				
Lymphotoxin-β receptor fusion protein	NCT01552681	Baminercept	Randomized, double-blind, placebo-controlled, phase II	Completed (90)
Inhibition of T cell–related cytokines: IL-21, IL-22	NA	NA	NA	NA

Abbreviation: NA, not available.

B and plasma cell depletion. In view of the remarkable B cell overactivity, B cell depletion and/or inhibition of B signals for B cell differentiation and survival appears to provide a reasonable therapeutic approach with beneficial results (42–48). Rituximab is a chimeric antibody directed against CD20 antigen leading to B cell depletion. As an additional mechanism for its action, recent data suggest T cell impairment, either due to decrease of B cell–derived proinflammatory cytokines and B cell antigen-presenting activity or due to hampered production of IL-17-producing T cells (49).

Although CD20 blockade was initially shown to be efficacious in alleviating mucosal dryness and systemic manifestations related to immunocomplex formation (purpura, peripheral neuropathy, and cryoglobulinemic vasculitis), refractory inflammatory arthritis (50), and fatigue (42), results from recent randomized clinical trials failed to reach the primary endpoints (47, 51) (**Table 1**). A recent meta-analysis on the efficacy of rituximab concluded that lacrimal gland function and, to a lesser extent, salivary flow improve following a single rituximab dose, but no differences were observed after 24 weeks regarding fatigue reduction, serious adverse events, quality-of-life improvement, and disease activity (52).

The reasons for rituximab failure could be related to patient selection and the implemented outcome measures, persistence of immunoglobulin-producing cells in parotid salivary glands (53), or codepletion of regulatory B cells. Additionally, the absence of CD20 from the long-lived plasma cells—the main producers of pathogenic autoantibodies (54)—could account for the observed treatment resistance (55). In this setting, the proteasome inhibitor bortezomib, a plasma cell depleter already licensed for the treatment of multiple myeloma, could have therapeutic potential for both refractory lupus and primary SS (56, 57).

In view of these observations and given the increasingly recognized variability of SS at both pathogenetic and phenotypic levels, identification of predictors of response to rituximab treatment would be crucial for the selection of appropriate patients for clinical trials. So far, data from two studies are apparently conflicting with respect to rituximab response in primary SS: A high baseline number of $CD20^+$ B cells/mm^2 in the parotid gland parenchyma predicted better responses (58), but an intense BAFF-driven B cell activation predicted poor response (59). Although this discrepancy could be related to differences in inclusion criteria, techniques implemented for the enumeration of B cells, or the origin of tissues examined (parotid versus MSGs), the different response indexes used have been thought to account for it. In the first study (58), EULAR (European League Against Rheumatism) SS disease activity index (ESSDAI)—an index of systemic disease activity—was implemented as a measure of rituximab efficacy; the second study (59) used a composite index mainly based on evaluation of glandular function and fatigue (60, 61). These data indirectly support previous views regarding the efficacy of rituximab in systemic B cell–driven rather than local disease.

BAFF/BAFF receptor (BAFF-R) axis. BAFF, a member of the TNF family, is essential for the development and survival of B lymphocytes. The development of a phenotype resembling human SS in BAFF-transgenic mice is highly suggestive of its pivotal role in disease pathogenesis (62). Recent data suggest that the expression of BAFF is tightly regulated by IFN regulatory factors, implying that abrogation of the type I signature by IFN inhibition could also lead to downregulation of BAFF expression (63, 64).

These observations provide support for targeting BAFF in SS patients with the monoclonal antibody belimumab, already licensed for patients with systemic lupus erythematosus. In a recent prospective one-year open-label bicentric study including 30 SS patients, 10 mg/kg of belimumab was administered at weeks 0, 2, and 4 and then every four weeks to week 24. The primary endpoint, assessed at week 28 and reached by 60% of patients, was improvement in two of five items:

reduction of ≥30% in dryness score on a visual analogue scale (VAS), ≥30% in VAS fatigue score, ≥30% in VAS pain score, ≥30% in VAS systemic activity as assessed by the physician, and/or improvement of >25% in any B cell activation biomarker values (65) (NCT01008982, **Table 1**). Almost 90% of the 15 patients who were responders at week 28 also responded at week 52. Improvements in the glandular, lymphadenopathy, and articular domains, as well as further decreases in RF titers, were observed at the end of follow-up, with salivary flow, Schirmer's test, and focus score of the salivary gland biopsy being unchanged (66). In a follow-up study, deterioration of clinical features was observed following cessation of belimumab therapy, along with increases in RF, IgM, and BAFF titers (67). Of note, belimumab treatment led to restoration of both transitional and naive B cell subsets—shown to be expanded at baseline—to levels similar to those observed in healthy donors and normalized BAFF-R expression levels. These changes were associated with decreases in serum levels of immunoglobulins, antinuclear antibodies, and RF, and with an increase in C4 complement levels (68).

Given that BAFF levels, as well genetic variants of both BAFF and BAFF-R (69–71), have been linked to SS-related lymphoma—previously shown to arise from RF-positive B cell clones (72)—belimumab treatment restricting the expansion of RF-positive B cells seems a promising therapeutic strategy for the subset of SS cases prone to or complicated by mucosa-associated lymphoid tissue (MALT) lymphoma.

Analysis of a subgroup of the BELISS study revealed that high blood and salivary NK cell numbers are associated with a worse response to belimumab (73), and high type I IFN scores at baseline are associated with improved outcomes (74). According to the authors, these findings possibly imply the existence of two distinct subsets of primary SS: one with a predominant type I IFN-BAFF-B cell axis, representing good responders to belimumab; and one with a predominant type II IFN-NK cell axis, representing nonresponders.

Data from our group (71), comparing a healthy population to patients with primary SS, revealed a high frequency of the functional BAFF-R mutation in SS patients, particularly associated with MALT lymphoma and early SS onset. This mutation leads to increased alternative NFκB signaling in B cells (71). In this context, administration of the BAFF-R inhibitor seems a rational therapeutic approach, especially for the subset of patients with documented activation of this signaling pathway. A single-dose randomized trial is currently under way (NCT02149420, **Table 1**).

CD20 and BAFF blockade. One of the current challenges in the treatment of SS is the lack of well-accepted strategies for the prevention of lymphoma among high-risk SS individuals, as well as the management of SS-related lymphoma. Despite the documented link of the BAFF/BAFF-R axis with SS-related lymphoma, preliminary observations imply that neoplastic lymphoproliferation is resistant to belimumab alone (68). Additionally, data derived from a murine model of human CD20 expression suggest that the local overexpression of BAFF in MALT tissues may hamper the effectiveness of rituximab, which only in combination with belimumab turned out to be efficacious on marginal zone B cells (75). These data, along with the previously shown upregulation of BAFF levels following rituximab treatment, imply the potential usefulness of combination therapy of belimumab with rituximab (76). In this context, a randomized trial is currently under way (NCT02631538, **Table 1**).

BCR signaling. The crucial role of BCR in B cell development, survival, proliferation, functional differentiation, and migration provides a novel rationale for targeting B cell signaling pathways in primary SS. Increasing evidence points to a critical role of a network of kinases such as spleen tyrosine kinase, phosphatidylinositol 3-kinase delta isoform (PI3Kδ), and Bruton's tyrosine kinase (BTK) in BCR signal transduction. Blockade of these kinases has recently been licensed for the

treatment of chronic lymphocytic leukemia (77). Recent data support activation of the PI3Kδ pathway in affected salivary gland tissues from an animal model of SS. Upon blockade of this pathway by UCB5857, a small-molecule inhibitor of PI3Kδ, investigators observed a decrease in lymphocytic infiltration and a disruption of lymphoid aggregates, implying a promising role of this agent in SS treatment (78). In view of these data, a randomized trial is under way (NCT02610543, **Table 1**). Moreover, BTK levels were shown to be increased in circulating B cells of a significant percentage of primary SS patients, in association with serum RF levels possibly decreasing thresholds for B cell activation, contributing to the observed B cell overactivity (79). Although BTK inhibitors have been tested in lymphoid malignancies, no data regarding their role in SS are available yet.

Targeting the B cell molecule CD22—a 135-kDa transmembrane sialoglycoprotein of the immunoglobulin superfamily—led to meaningful clinical responses in regard to fatigue, patient and physician global assessments, and a composite score including Schirmer-I test, unstimulated whole salivary flow, fatigue, erythrocyte sedimentation rate (ESR), and IgG. The beneficial effect of epratuzumab might be related to its dual functional role as a homing receptor for recirculating B cells and as a down-modulating coreceptor for BCR (80).

Ectopic Germinal Center Formation

Ectopic germinal centers, defined as aggregates of B cells surrounded by T cells, denote active inflammation at the site of secondary lymphoid organs and involve somatic hypermutation, BCR editing, and immunoglobulin class switching. Their formation under normal circumstances demands close cooperation between follicular dendritic cells and IL-21-producing CD4-T follicular cells, which provide the signals for B cell activation and migration into the follicle, with IL-21 functioning as a potent inducer of plasma cell formation and contributor in germinal center B cell selection (81).

The formation of ectopic germinal centers is increasingly recognized as a crucial mechanism in the pathogenesis of SS and other systemic autoimmune diseases. In patients with primary SS, their prevalence varies between studies from 18% to 59%. Nevertheless, it is increasingly recognized that germinal center formation in the setting of SS is associated with higher focus scores, RF positivity, and anti-Ro/La positivity and is viewed as a marker of lymphoma development (82, 83).

Germinal center formation in the setting of SS remains largely unexplored, although recent advances point toward several underlying pathogenetic mechanisms. Genetic data revealed that variants of the C-X-C chemokine receptor locus 5 (CXCL5)—a B cell receptor for the lymphoattractant chemokine CXCL13—increase SS susceptibility (36). Moreover, increased numbers of CD4-T follicular helper cells, shown to redirect B cell differentiation toward memory B cells and plasma cells, were identified in salivary gland tissues from primary SS patients in association with increased focus scores and extraglandular manifestations (84) and a network of follicular dendritic cells (85). Last, a wide variety of molecules known to play a key role in the formation and maintenance of germinal center–like structures—including cytokines such as IL-21 and IL-22, chemokines CCL19 and CCL21, and chemokine receptors CXCL12 and CXCL13—have all been associated with SS development (86). The fact that Th17 cells (a newly identified $CD4^+$ Th subtype implicated in the pathogenesis of SS) are a major source of IL-21 and IL-22 seems to provide a rationale for targeting these cells in future SS therapeutic interventions (87, 88).

Previous data suggested that lymphotoxin-β receptor blockade in the NOD mouse model of SS led to reduction of B cell accumulation in lacrimal glands, together with the chemoattractant molecule CXCL13 (89). In accord with these observations, administration of baminercept—a

lymphotoxin-β receptor fusion protein—in a cohort of primary SS patients led to significant reduction in the disease activity index ESSDAI, with no detectable meaningful effect in sicca-related features. Because some cases of liver injury were reported, further data are warranted (90) (NCT01552681, **Table 1**).

CONCLUSION

Given the remarkable heterogeneity of SS, elucidation of distinct operating pathways at both peripheral and salivary gland tissue levels in relation to diverse clinical phenotypes remains a major challenge, particularly for a subgroup of patients prone to lymphoma development. As a consequence of this complexity, selection of the optimal therapeutic intervention is a second important challenge. Molecular events promoting antigen presentation, costimulation, and B cell function and survival, as well as the formation of ectopic germinal centers at the site of inflamed tissues, are currently considered key players in disease pathogenesis and therefore promising therapeutic targets. Inhibitors of cathepsin S, B7-related molecules and CD40, abatacept, BAFF, CD20 and CD22 blockers, and PI3Kδ and lymphotoxin-β receptor repressors are currently the main therapeutic weapons under investigation. The efficacy, short- and long-term safety, and duration of treatment with these agents, as well as the identification of reliable and consistent biomarkers of response, remain to be explored in multicenter controlled studies.

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