hazard ratio explained by the difference in MRD-negative rates could potentially be higher.

So, how can this model be used in future clinical trials? Clearly, the model will not be useful for comparing a chemoimmunotherapy regimen with a targeted therapy, such as ibrutinib, which rarely achieves MRD negativity and is given indefinitely as maintenance therapy. In contrast, it may have usefulness in informing sample-size calculations based on MRD negativity end points for studies comparing chemoimmunotherapy with novel regimens that have significant potential to achieve MRD negativity. In particular, venetoclax plus obinutuzumab,[8] venetoclax plus ibrutinib,[9] and venetoclax plus ibrutinib and obinutuzumab[10] in the first-line setting have been shown to achieve high rates of MRD negativity. Three venetoclax-based regimens are currently being compared with chemoimmunotherapy in the ongoing first-line CLL13 trial (NCT02950051). This study uses MRD negativity at 15 months as the primary end point to compare the venetoclax plus obinutuzumab (which is given for 1 year) and chemoimmunotherapy arms. One caveat is that the model discussed here is based entirely on studies of chemoimmunotherapy. It is unknown whether the relationship between treatment effect on MRD negativity and treatment effect on PFS will be quantitatively similar in patients receiving venetoclax-based regimens given for a finite duration. For this reason, it will be important to repeat the analyses performed by Dimier et al when sufficient data on venetoclax-based regimens are available. Finally, as more sensitive technologies for MRD detection (eg, high-throughput sequencing) are adopted, the quantitative impact of MRD negativity on PFS hazard ratio will need to be reassessed.

We now possess an array of therapeutic options able to achieve deep responses; the ability to rapidly determine significant differences between treatment arms, through quantitative detection of MRD, is essential to accelerate the regulatory approval of novel regimens and make them widely available for the benefit of our patients.

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Rowczenio et al, page 974

The elusive pathogenesis of Schnitzler syndrome

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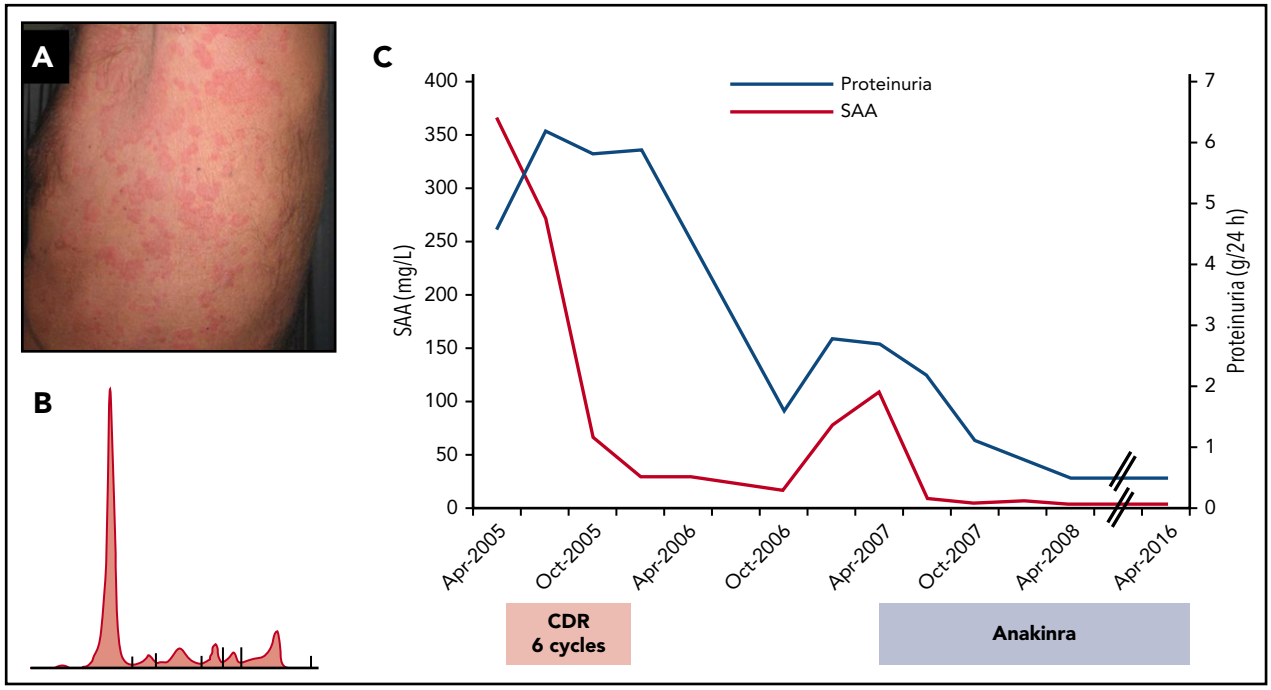
In this issue of *Blood*, Rowczenio et al investigate the role of genetic factors, inflammasome activation, and proinflammatory cytokines in the pathogenesis of Schnitzler syndrome.[1]

Schnitzler syndrome is a rare disorder characterized by recurrent or chronic urticaria associated with a monoclonal gammopathy and persistent inflammation.[2] This disorder often goes undiagnosed.[3] The rash is typically resistant to antihistamines, and histologically, it is a neutrophilic urticarial dermatosis. The monoclonal protein is an immunoglobulin Mκ (IgMκ) in 80% to 90% of cases. In the remaining patients, IgMλ and IgG monoclonal proteins have been reported. The invariable presence of the monoclonal protein suggests a possible pathogenic role, which has remained elusive. Additional features, which are minor diagnostic criteria, include intermittent fever, arthralgia, bone pain, liver or spleen enlargement, palpable adenopathy, elevated markers of inflammation, and bone abnormalities on radiological investigations. Fatigue is frequent, and the clinical manifestations are often disabling. Schnitzler syndrome can progress to Waldenström macroglobulinemia or other lymphoproliferative disorders, with a frequency comparable to that of patients with IgM monoclonal gammopathy of undetermined significance. Moreover, systemic amyloid A (AA) amyloidosis that occurs as a consequence of chronic inflammation may develop (see figure). To prevent this, treatment should be aimed at



Clinical presentation and course of a patient with Schnitzler syndrome and reactive AA amyloidosis treated with anticlone therapy followed by IL-1 blocking treatment. A 55-year-old man was diagnosed with amyloidosis by renal biopsy. (A) During the previous 30 years, he had chronic nonpruritic urticarial rash associated with recurrent fever (up to 39°C) and arthralgia. Proteinuria and subsequent nephrotic syndrome were associated with profound postural hypotension and diarrhea. (B) A small (8 g/L) IgMκ monoclonal protein was detected with a 6% clonal bone marrow lymphoplasmacytic infiltrate. Proteinuria was 4.6 g per 24 hours, and there were no signs of amyloid cardiac or liver involvement. Amyloid deposits were detected in the abdominal fat, which reacted with anti-serum amyloid A (anti-SAA) apolipoprotein antibodies and not with anti-κ and anti-λ light chain antibodies. (C) A diagnosis of AA amyloidosis due to Schnitzler syndrome with kidney and autonomic nervous system involvement was made, and the patient was treated with cyclophosphamide, rituximab, and dexamethasone, with improvement of clinical symptoms and reduction of SAA and proteinuria. After 18 months, an increase in SAA and proteinuria accompanied an exacerbation of symptoms, and the patient was placed on anakinra, resulting in complete clinical remission and normalization of SAA and proteinuria. Apr, April; CDR, cyclophosphamide, rituximab, and dexamethasone; Oct, October; SAA, serum amyloid A.

reducing the concentration of serum amyloid A apolipoprotein, even in patients with moderate or controlled symptoms. Light chain amyloidosis is a theoretical possibility, although no cases have been reported so far.

Inflammation and proinflammatory cytokines, particularly interleukin-1β (IL-1β), play a key role in the pathogenesis of Schnitzler syndrome, and treatment with the IL-1 receptor antagonist anakinra results in complete control of symptoms in more than 80% of patients.[4] Other IL-1 blocking approaches, such as canakinumab, an anti-IL-1β antibody, and rilonacept, a fusion protein consisting of the ligand-binding domains of IL-1 receptor and IL-1 receptor accessory protein fused to the Fc region of human IgG1 that binds and neutralizes IL-1, have shown promising activity.[2] Although IL-1 blocking therapy dramatically improves quality of life, it is not curative and probably does not prevent the development of lymphoproliferative disorders. Schnitzler syndrome apparently is an acquired autoinflammatory disease. Autoinflammatory diseases, an ever-expanding universe, are caused by acquired or hereditary dysregulation of the innate immune system. The hereditary disorders are caused by many mechanisms, including inappropriate inflammasome-mediated production of the cytokine IL-1β and perturbations in signaling by the transcription nuclear factor κB, ubiquitination, cytokine signaling, and protein folding.[5] Although it can be discriminated on a clinical basis,[6] the presentation of Schnitzler syndrome is very similar to that of the hereditary autoinflammatory disease cryopyrin-associated periodic syndromes (CAPS). This condition is caused by activating mutations in the *NLRP3* gene (nucleotide-binding oligomerization domain-leucine-rich repeats containing pyrin domain 3). Indeed, the common variant *NLRP3*p.V198M was found in 2 patients with classical (IgM) Schnitzler syndrome, and somatic *NLRP3* mosaicism was identified in the myeloid lineage of 2 patients with variant (IgG) Schnitzler syndrome. On the basis of these findings, Rowczenio and colleagues performed a next-generation sequencing-based search for mutations in *NLRP3* and 32 other genes associated with monogenic autoinflammatory diseases in 21 patients with Schnitzler syndrome. Their search confirmed the presence of the *NLRP3*p.V198M variant in 1 patient that was previously reported, but no additional predisposing abnormalities in *NLRP3* or in the other 32 targeted genes were detected. However, Rowczenio and colleagues found higher levels of apoptosis-associated speck-like protein with Card domain aggregates, IL-6, and IL-18 in the sera of their 21 patients, in comparison with controls, which were similar to levels measured in CAPS patients. This clearly indicates the activation of inflammasome. However, the mechanism of this activation remains obscure. The authors report a series of rare allele variants in the 32 targeted genes, some of which are listed in the registry of hereditary autoinflammatory disorders mutations, but their clinical significance is currently unknown. Future studies will elucidate the possible role of genetic factors in Schnitzler syndrome.

The interplay between the lymphoplasmacytic clone and the activation of the inflammasome remains elusive, and it

is possible that different manifestations can have different causes. For example, high levels of vascular endothelial growth factor, which decrease in successfully treated patients, and markers of bone formation, such as osteocalcin and bone-specific alkaline phosphatase, can underlie or reflect bone alterations.[7] Also, it has been speculated that IL-1 stimulation may facilitate the onset of the lymphoplasmacytic clone through interactions between IL-1 receptor complex and IL-1 receptor-associated kinase with MYD88.[2] The rarity of Schnitzler syndrome makes it extremely difficult to conduct large studies in this disorder, and international collaboration is crucial. However, the elucidation of the complex mechanisms underlying this fascinating disease may shed light on other autoinflammatory disorders and rare monoclonal gammopathies of clinical significance.

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LYMPHOID NEOPLASIA

Comment on Ren et al, page 982

R-spondin(g) to syndecan-1 in myeloma

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In this issue of *Blood*, Ren et al investigate mechanisms underlying a novel strategy to block multiple myeloma (MM) cell proliferation by targeting the heparin sulfate (HS) proteoglycan syndecan-1 and identify the Wnt/β-catenin pathway as a critical mediator of this approach. If validated, these findings could lead to new therapeutic strategies in MM that may be particularly effective in circumventing microenvironmental forms of resistance in this disorder.[1]

MM is an accumulative disease of mature plasma cells, and during the last several years, major therapeutic advances in this disease have emerged, including the introduction of novel proteasome inhibitors, immunomodulatory agents (IMiDs; eg, pomalidomide), and antibodies (eg, daratumumab, SLAM7).[2] Nevertheless, despite these advances, the disease remains incurable for many patients, and new and more effective therapies are clearly needed. Notably, aside from intrinsic or acquired forms of drug refractoriness, stromal cell and other microenvironmental forms of resistance are widely believed to represent a continuing impediment to curative efforts.[3]

Syndecan-1 is a membrane-bound HS proteoglycan, which is an extracellular matrix or cell membrane–bound glycoprotein that binds to and regulates the activity of soluble protein ligands involved in regulation of cell signals related to growth, survival, differentiation, and tumorigenesis.[4] It has been previously shown to be highly expressed in plasma cells and to play a role in mediating MM cell interactions with the bone marrow niche.[5] Decoration of syndecan-1 by HS chains has been linked to multiple effects, including activation (via Frizzled) of the Wnt/β-catenin pathway, which operates upstream of c-Myc and cyclin D1, both of which are implicated in MM pathogenesis. In this context, R-spondins represent proteins secreted by the microenvironment that act as highly potent activators of Wnt/β-catenin signaling. Using genetic techniques, Ren et al found that loss of HS (by knocking down the HS copolymerase EXT1 by CRISPR/Cas9 or by coadministering heparitinase, which degrades HS) blocked Wnt/β-catenin pathway signaling and downregulated downstream targets in both MM cell lines and primary samples. Significantly, growth attenuation primarily reflected proliferation inhibition and could not be reversed by stromal cell coculture. Importantly, genetic manipulation via constitutively active β-catenin or c-Myc overexpression reduced antiproliferative effects of these interventions, demonstrating their functional significance in HS/syndecan-1 growth signaling. Of note, the paracrine effects of Wnt signaling could be recapitulated in stromal cells, which have been demonstrated to be a source of Wnt ligands.[6] In support of this notion, the authors demonstrated that (pre)osteoclast-secreted R-spondins potently induced Wnt signaling and that this event could be antagonized by genetic or pharmacologic prevention of HS decoration of syndecan-1. The authors conclude that interventions disrupting HS-mediated activation of syndecan-1 and Wnt/β-catenin signaling pathway may represent a new and effective approach to circumventing bone marrow niche–related MM cell proliferation. A summary of the relevant pathways involved in these interactions is shown in the figure.

Although the findings by Ren et al could provide a novel framework for targeting MM by disabling a potentially important pathway implicated in microenvironmental signals, the study raises a number of questions, the resolution of which will be important in successfully translating this concept to the clinic. For example, it