Btk, both targets of dasatinib (see figure), are critically involved in various neutrophil activation pathways.

In the present study, the authors studied the effect of dasatinib on functional responses of human and murine neutrophils using in vitro and ex vivo assays.1 The potency of dasatinib to inhibit both integrin-dependent and Fc-receptor-dependent neutrophil activation at low concentrations (IC50 ranging from 9–50nM depending on the stimulus) is striking. These receptors share the immunoreceptor tyrosine activation motif (ITAM) mode of activating neutrophils via Src family kinases and Syk (see figure).8 Low nanomolar concentrations of dasatinib inhibited the phosphorylation of Syk and also reduced Syk-dependent cell functions including spreading, adhesion, and exocytosis of secondary granules. However, dasatinib did affect PMA-mediated spreading, suggesting that the drug does not influence the cytoskeletal machinery. As Src family kinases are upstream of Syk in integrin-mediated outside-in signaling,8 it is likely that dasatinib inhibits the activation of Src family kinases (not investigated by Abram and Lowell in this study8) and only indirectly reduces phosphorylation of Syk and other downstream targets. Further studies have to address the question of which of the Src family kinases are inhibited in neutrophils by dasatinib, because some protein tyrosine kinases have a unique function in neutrophil activation, whereas other protein tyrosine kinases have overlapping or redundant functions.9,10

Interestingly, low nanomolar concentrations of dasatinib partially inhibited fMLP-induced responses, whereas G-protein-coupled receptor-mediated functions were predominantly not affected by dasatinib. Chemotaxis, adhesion, and migration are all β2-integrin-dependent processes. However, dasatinib only reduced chemotaxis and adhesion but did not affect migration through membranes, suggesting that several protein tyrosine kinases are involved in the different steps. Future studies have to identify the protein tyrosine kinases involved in the different steps. One strength of the current study is its use of dasatinib in clinically relevant concentrations, supporting the notion that some neutrophil functions are inhibited during dasatinib treatment. Here, oral administration of 5 mg/kg of dasatinib to mice significantly reduced tumor necrosis factor-α–induced leukocyte adhesion to FCS-coated surface.

The fact that dasatinib reduces neutrophil adhesion but has no major effect on phagocytosis or killing bacteria suggests that the increased infection rate in patients treated with dasatinib is because of reduced neutrophil recruitment into injured tissue.

Futosi et al attribute the effects of dasatinib to its inhibition of Src family kinases, a critical nonreceptor kinase directly involved in integrin- and Fc-receptor signaling as well as in stabilization of neutrophil adhesion.1 It will be interesting in the future to study bosutinib, which also inhibits Src family kinases but likely not neutrophil Btk, together with dasatinib. These studies will show how much neutrophil inhibition is specifically related to Src family kinase inhibition, and whether bosutinib carries a lower infection rate than dasatinib. The study by Futosi et al provides further proof that neutrophil nonreceptor protein tyrosine kinases, such as the Src family kinases or Syk, may be excellent targets for therapy of chronic inflammatory diseases.1 However, the use of kinase inhibitors in chronic inflammatory disease may require greater selectivity for the target kinase to limit the off-target kinase–induced side effects.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES


Comment on Kuo et al, page 4838


Peter Möller and Andreas Viardot

Two decades after the first cure of Helicobacter pylori (Hp)–associated marginal zone B-cell lymphoma of the stomach by eradicating the bacterium,1 it is still amazing to witness the success of this treatment in a high proportion of patients. However, it works is still unclear. The most logical hypothesis, that the lymphoma is driven through tonic B-cell receptor triggering by some Hp antigen, has not been proven. Alternatively, T-cell dependency of this slowly growing lymphoma has been suggested. Antibiotics may decrease the bacteria-sustained mucosal T-cell response, thereby preventing the cytokine production needed to sustain the lymphoma.2 But how does this explain lymphoma regression in perigastric lymph nodes that are normally crammed with T cells? And what accounts for the efficacy of antibiotics in the absence of Hp?3

This lack of mechanistic explanation has not kept hemat-oncologists from trying to see

**Clinical Trials**

Comment on Kuo et al, page 4838


Peter Möller and Andreas Viardot

Two decades after the first cure of Helicobacter pylori (Hp)–associated marginal zone B-cell lymphoma of the stomach by eradicating the bacterium,1 it is still amazing to witness the success of this treatment in a high proportion of patients. However, it works is still unclear. The most logical hypothesis, that the lymphoma is driven through tonic B-cell receptor triggering by some Hp antigen, has not been proven. Alternatively, T-cell dependency of this slowly growing lymphoma has been suggested. Antibiotics may decrease the bacteria-sustained mucosal T-cell response, thereby preventing the cytokine production needed to sustain the lymphoma.2 But how does this explain lymphoma regression in perigastric lymph nodes that are normally crammed with T cells? And what accounts for the efficacy of antibiotics in the absence of Hp?3

This lack of mechanistic explanation has not kept hemat-oncologists from trying to see
whether or not *Hp* eradication had a beneficial effect on aggressive, large-cell gastric B-cell lymphomas. And, yes, it had. Both large-cell lymphoma evolving into gastric marginal zone B-cell lymphoma and “de novo” large-cell gastric B-cell lymphoma have regressed on antibiotic treatment, as cited in this issue of *Blood* in Kuo et al.4

Kuo and colleagues report a series of patients diagnosed with stage IE and stage IIE *Hp*-positive gastric diffuse large B-cell lymphoma (DLBCL) with and without a coexisting marginal-zone B-cell component of mucosa-associated lymphoid tissue (MALT) type treated with antibiotic *Hp* eradication therapy. The reported cure rates are amazing: 18 of 32 combined marginal-zone and DLBCLs and 11 of 16 pure DLBCLs were cured, with time to remission ranging between 0.6 and 7.5 months. Except for 1 patient who relapsed in the lung, all others stayed free from disease during a mean follow-up of 7.7 years. Those patients who failed to respond to antibiotics as verified by frequent follow-up by gastroscopies with biopsies were treated with standard chemotherpay. Given the excellent results of combined standard therapy in gastric DLBCL,3 the risk taken by delaying standard treatment onset is fairly low. And the benefit in case of antibiotic efficacy is substantial, given the toxicity of chemotherapy in this largely elderly population.

The fact that more than half of the patients with gastric large B-cell lymphoma were cured by antibiotics underscores its peculiarity within the comprehensive group of DLBCL. This observation fits the growing cytogenetic and expression signature evidence that most (but not all) gastric large-cell lymphomas are transformed marginal-zone B-cell lymphomas.6-8

The cure rate of gastric large B-cell lymphoma with antibiotics might be even higher if this large-cell marginal-zone lymphoma could be reliably diagnosed as such. At present, this is difficult because hematopathologists have not yet agreed on a specific immunophenotype for it and sorting out the DLBCL subtypes as defined by the World Health Organization classification would presently require comprehensive gene probe analysis. Even so, the series reported by Kuo et al is a solid base for initiating a multicenter trial testing antibiotics as first-line therapy (followed by rescue chemotherapy in case of unresponsiveness) against current standard protocols (combination of an anthracycline-based chemotherapy and rituximab with or without consolidation radiotherapy9), for example, adverse effects and quality of life.

**Conflict of interest disclosure:** The authors declare no competing financial interests.

**REFERENCES**


Peter Möller and Andreas Viardot