Rituximab: late-onset neutropenia, sometimes more than 6 months after stopping treatment (continued)

● Among 104 reports to French regional pharmacovigilance centres involving severe late-onset neutropenia linked to *rituximab*, the time to onset varied from 1.5 to 15 months after the last dose. These cases of neutropenia expose patients to a risk of serious infections.

Rituximab (Mabthera° or other brands) is a monoclonal antibody directed against the CD20 antigen present on the surface of B lymphocytes (both normal and malignant) which causes these cells to die (1). It is used as a cytotoxic drug in some types of haematological cancer, and as an immunosuppressant, particularly in rheumatoid arthritis and pemphigus vulgaris (2,3). *Rituximab* carries a risk of late-onset neutropenia, so called because it often develops weeks or even months after administration of the last dose (1,4-6).

Several French regional pharmacovigilance centres identified and then analysed reports in the French pharmacovigilance database concerning neutropenia attributed to *rituximab*, defined as a blood neutrophil count below 109/litre, i.e. 1000 per mm^3 (4,7).

Among the 320 cases of neutropenia attributed to *rituximab* identified between 2000 and 2019, 110 were observed at least 6 weeks after the last infusion.

These cases of late-onset neutropenia involved 60 men and 50 women, with an average age of 62 years. Among the 104 patients with severe neutropenia, 84 were admitted to hospital or had their hospital stay extended. For 5 patients, the notifier considered that their condition was life-threatening (no details provided), and for 15 others, there were additional aggravating risk factors. The mean interval between the last dose of *rituximab* and onset was about 3.5 months, with extreme values ranging from about 1.5 to 15 months. 89 patients had late-onset neutropenia with a neutrophil count below 500 per mm^3 and another 21 patients had a neutrophil count between 500 and 900 per mm^3. The outcome was favourable in 73 patients, while 20 others (18%) had not recovered at the time the report was submitted. The authors did not provide details on the outcome in the other cases (7).

The 2021 European summary of product characteristics (SPC) for medicinal products based on *rituximab* mentions late-onset and persistent neutropenia, sometimes associated with severe and fatal infections, and recommends regular monitoring of blood neutrophil count up to 6 months after treatment cessation or if there is any sign of infection (2).

The mechanisms leading to late-onset neutropenia linked to *rituximab* are unknown. Direct toxicity is considered to be unlikely. Myeloid maturation arrest has been observed in some patients (6). When this disorder is accompanied by clinical signs, they usually take the form of fever, mouth ulcers, or gingival inflammation (6). *Ocrelizumab* and *obinutuzumab*, anti-CD20 monoclonal antibodies like *rituximab*, also carry a risk of late-onset neutropenia, sometimes occurring several months after treatment cessation (1,8).

IN PRACTICE In patients who have received *rituximab*, neutropenia can sometimes develop more than 6 months after the last dose, exposing patients to the risk of sometimes severe infections, even long after stopping treatment. This justifies performing neutrophil counts regularly, e.g. every month, for several months after the last infusion, or if there is any suspicion of infection. This information should be given to patients, and they and their family or carers should be urged to look out for any sign of fever, mouth ulcers or gingival inflammation occurring in the months following cessation of *rituximab* treatment.

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