

Management of immune thrombocytopenia in multiple sclerosis patients treated with alemtuzumab: a Belgian consensus

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SUMMARY

Alemtuzumab (Lemtrada[®]) is a humanised monoclonal antibody indicated for the treatment of adult patients with relapsing/remitting multiple sclerosis with active disease defined by clinical or imaging features. Alemtuzumab demonstrated superior efficacy over active comparator in both treatment naive patients and those with inadequate response to prior therapy. Alemtuzumab is associated with a consistent and manageable safety and tolerability profile. Treatment with alemtuzumab for multiple sclerosis increases the risk for autoimmune adverse events including immune thrombocytopenia. Complete blood counts with differential should be obtained prior to initiation of treatment and at monthly intervals thereafter for 48 months after the last infusion. After this period of time, testing should be performed based on clinical findings suggestive of immune thrombocytopenia. If immune thrombocytopenia onset is confirmed, appropriate medical intervention should be promptly initiated, including immediate referral to a specialist. This paper presents the consensus of Belgian multiple sclerosis specialists and haematologists to guide the treating physician with practical recommendations.

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INTRODUCTION

Alemtuzumab (Lemtrada[®]) is a humanised monoclonal antibody approved in more than 60 countries. Within the European Union, alemtuzumab is indicated for the treatment

of adult patients with relapsing-remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features. LEMTRADA is not recommended for patients with inactive disease or those stable on current therapy.

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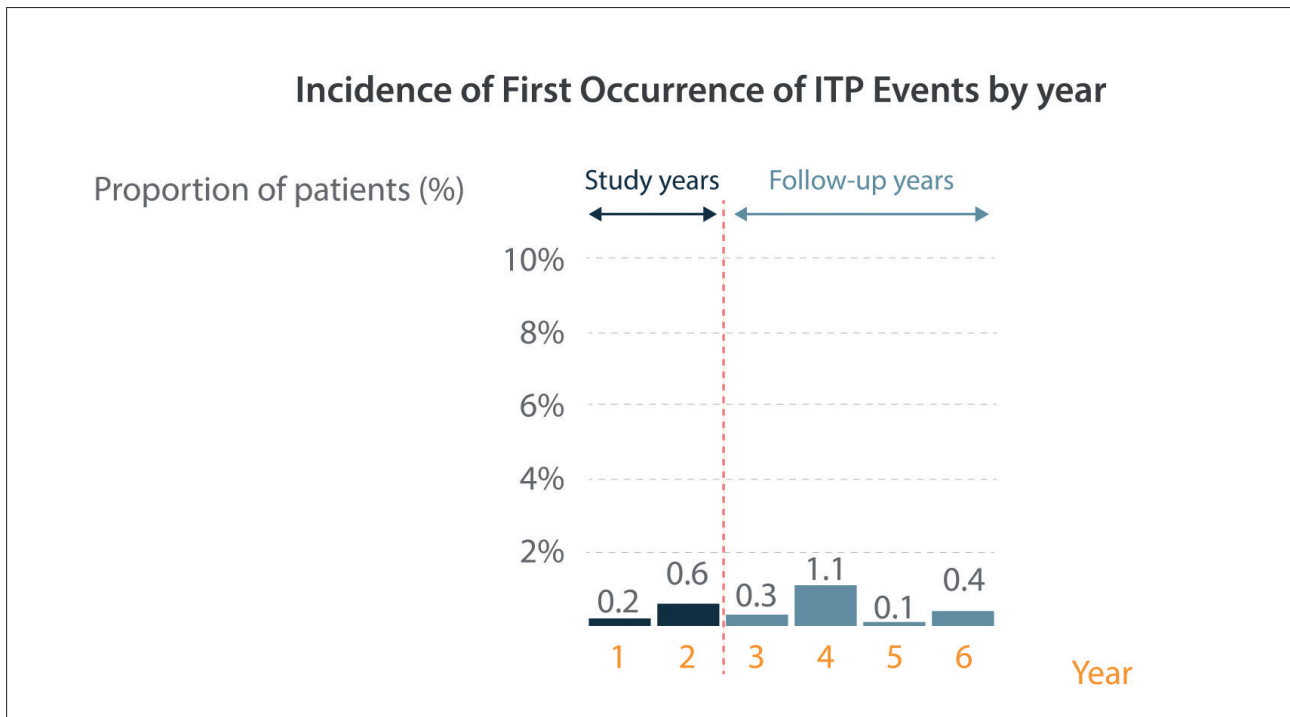


FIGURE 1. Incidence of first occurrence of ITP by year in the CARE-MS study.

Alemtuzumab demonstrated superior efficacy over active comparator in both treatment naive patients and those with inadequate response to prior therapy. Alemtuzumab is associated with a consistent and manageable safety and tolerability profile.¹ The most recent efficacy data over six years on clinical and MRI lesion activity as well as on brain volume loss suggest that alemtuzumab may provide a unique treatment approach for RRMS patients, offering durable efficacy in the absence of continuous treatment.²

Treatment with alemtuzumab for multiple sclerosis (MS) increases the risk for autoimmune adverse events including immune thrombocytopenia (ITP) previously known as Immune Thrombocytopenic Purpura.³⁻⁵

A first case of ITP after alemtuzumab occurred unexpectedly in the phase II study in MS and resulted in a fatal outcome.⁴ A Risk Management Plan (RMP) put in place ensured early detection of symptoms or signs of autoimmune disease, with the aim of minimising the impact of alemtuzumab-associated autoimmune effects.

The European risk management plan includes complete blood counts with differential which should be obtained prior to initiation of treatment and at monthly intervals thereafter for 48 months after the last infusion. After this period of time, testing should be performed based on clinical findings suggestive of ITP. If ITP is suspected, a complete blood count should be obtained immediately. At the time of treatment with Alemtuzumab, the patient should be educated to

remain vigilant for bleeding symptoms.⁶⁻⁸ In the event of an abnormal platelet count the sequence of additional tests and the appropriate moment to refer the patient to a haematologist will be at the discretion of the treating physician. If ITP onset is confirmed, appropriate medical intervention should be promptly initiated, including immediate referral to a specialist. This paper presents the consensus of Belgian MS specialists and haematologists to guide the treating physician with practical recommendations.

ALEMTUZUMAB AND ITP

ITP after receiving alemtuzumab has been described as a specific form characterised by delayed onset, responsiveness to conventional ITP therapies, and prolonged remission.⁵

Autoimmune adverse events were detected in MS patients treated with alemtuzumab in clinical trials.⁸ The six year follow up data of the CARE-MS studies were presented atECTRIMS 2016 and showed the following frequencies: 39% of alemtuzumab treated subjects experienced an autoimmune thyroid disorder, 2,6% an immune thrombocytopenia and 0,2% (two cases) an autoimmune renal disease. The incidence of first occurrence of ITP by year is shown in Figure 1.⁹

From all cases of thrombocytopenia detected in the phase III trials, 80% was by monthly blood monitoring and 20% by patient recognition of clinical symptoms.¹⁰

In post-marketing use through February 2017, 13.000 patients have been treated worldwide with alemtuzumab for

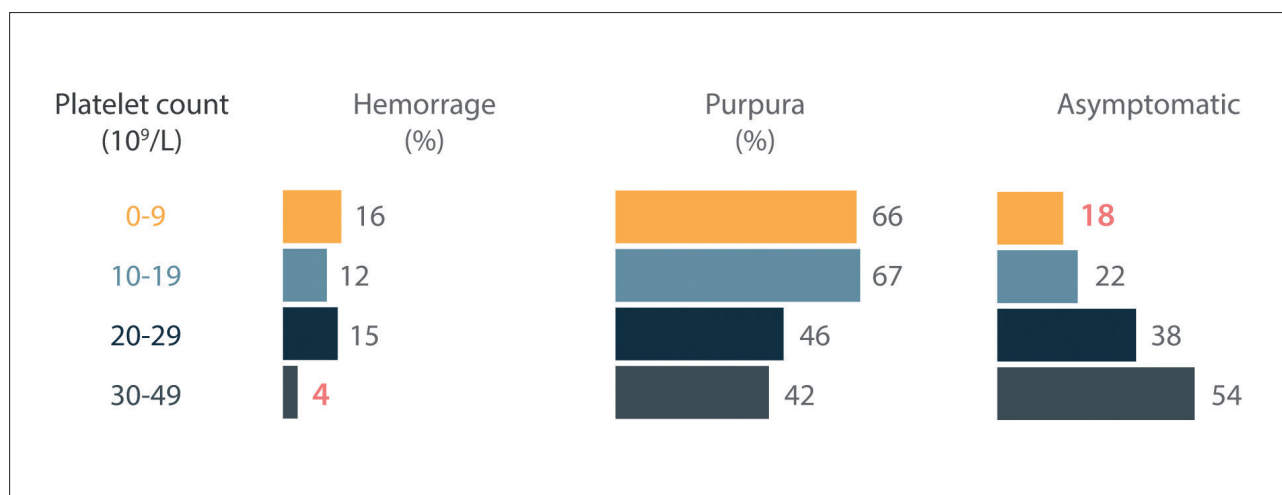


FIGURE 2. Bleeding symptoms are heterogeneous in ITP.

MS and the frequency for ITP has been estimated at 0.58%.¹¹ Post-marketing frequencies are not directly comparable to clinical trial incidences because of differences in ascertainment methodology and follow-up duration, and limitations of post-marketing reporting.

RECOMMENDATIONS FOR THE FOLLOW-UP OF PLATELET COUNTS IN PATIENTS TREATED WITH ALEMTUZUMAB BEFORE STARTING TREATMENT WITH ALEMTUZUMAB

Complete blood count (CBC) with differential should be obtained prior to initiation of Alemtuzumab (treatment and pre-phase with steroids).⁷

There are no data available about initiation of alemtuzumab in patients with low platelet count.

ONCE TREATED WITH ALEMTUZUMAB: MONITORING OF PLATELET COUNT

Complete blood count with differential should be obtained at monthly intervals thereafter for 48 months after the last infusion. After this period of time, testing should be performed based on clinical findings suggestive of ITP. If ITP is suspected a CBC should be obtained immediately.⁷

BLEEDING RISK AND PLATELET COUNT

It's also important to realise that there is no linear relationship between platelet count and bleeding symptoms. However, severe bleeding usually occurs with a platelet count below 10000/ μ L (Figure 2).^{12,13}

If ITP onset is confirmed, appropriate medical intervention should be promptly initiated, including immediate referral to a specialist. The following consensus goes beyond alem-

tuzumab's SmPC and aims to guide treating physicians on the necessary actions in case of an abnormal platelet count and before ITP is confirmed. Reference is made to the guidelines elaborated by the Belgian Hematological Society (BHS) for treating primary ITP in adults.¹⁴

EDUCATION OF THE PATIENTS

It's imperative to educate the patient to be vigilant for any clinical sign suggestive of bleeding between the monthly CBC checks. In case of such a sign, the CBC must be obtained immediately.

These suggestive clinical findings are described as follows: the observation of small scattered red, pink, or purple spots on the skin (petechiae); easy bruising; bleeding from a cut that is harder to stop; heavier, longer or more frequent menstrual periods than normal; bleeding between menstrual periods; bleeding from the gums or nose that is new or takes longer than usual to stop; or coughing up blood. Any of these should prompt further action including immediate referral to a specialist (Figure 3).⁷

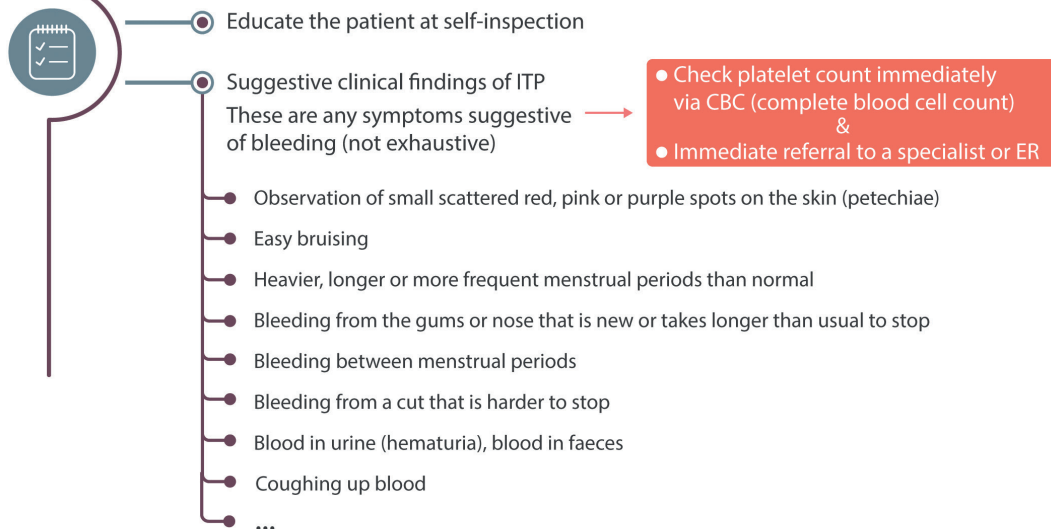
VALUES FOR REFERRAL AND DIAGNOSTIC WORK-UP (FIGURE 3)

Figure 3 describes which action to undertake depending on the platelet count received after every CBC check.

- When the platelet count is at least 150.000/ μ L: continue the monthly blood platelet count and bleeding symptoms surveillance
- Any steep decrease of 50% or more from previous value but still above 100.000/ μ L must prompt an immediate recheck of the CBC to exclude pseudothrombocytopenia (platelet aggregates). Contact the haematologist when this steep decrease is confirmed.

Management of ITP related to Lemtrada treatment

Clinical findings



Lab test

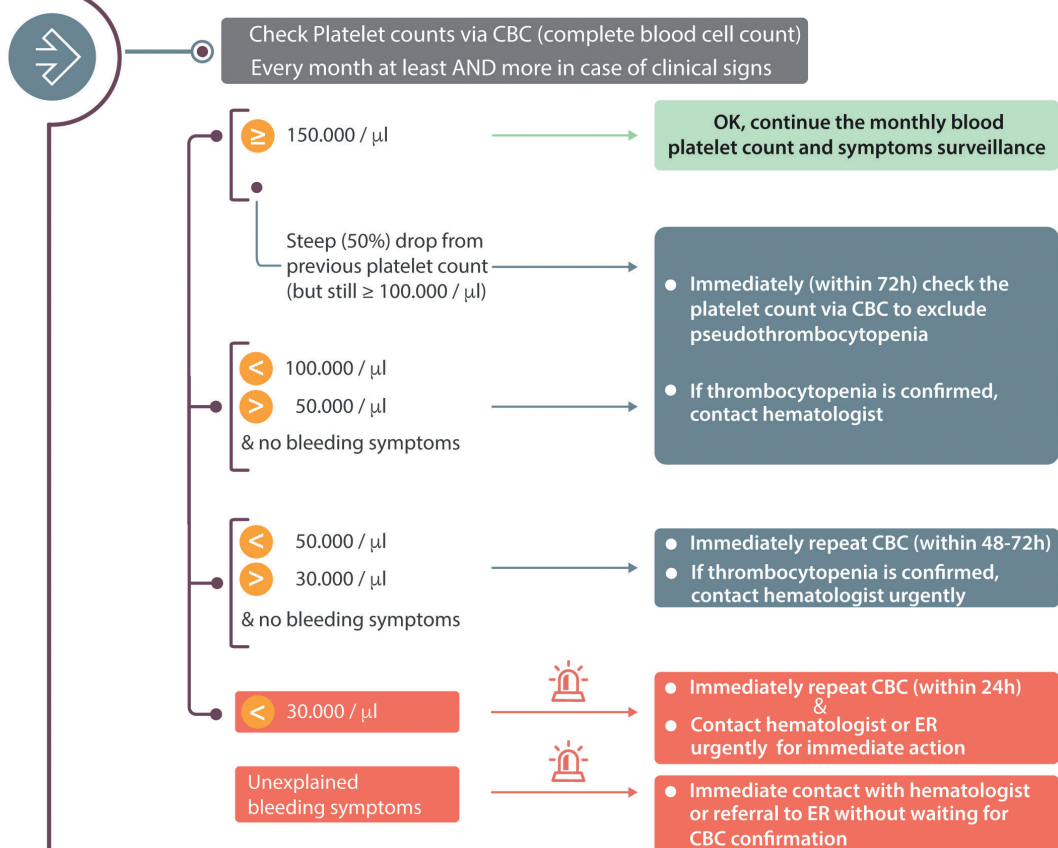


FIGURE 3. Recommendations for the follow-up of platelet counts in patients treated with alemtuzumab.

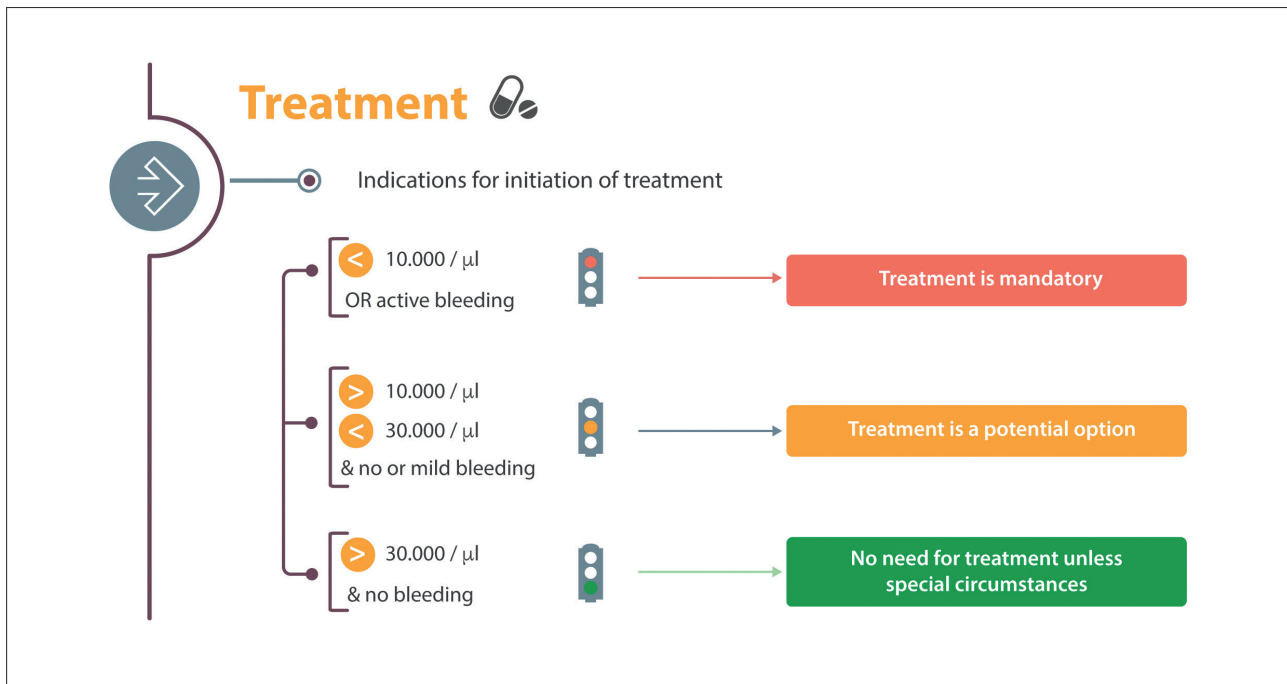


FIGURE 4. Management of ITP related to Lemtrada treatment.

- Pseudothrombocytopenia (platelet aggregates) has to be excluded by checking the platelets on EDTA, heparin, or citrate anticoagulated blood. A peripheral blood smear must exclude platelet clumping or aggregation.

- When the count is below $100.000/\mu\text{l}$ and still above $50.000/\mu\text{l}$ and with no bleeding symptoms, check the platelet count via a new CBC within 72h to exclude pseudothrombocytopenia. If thrombocytopenia is confirmed, contact the haematologist to discuss referral.
- With a value between 30.000 and $50.000/\mu\text{l}$ and no bleeding symptoms: recheck the CBC within 48-72h to exclude pseudothrombocytopenia and contact the haematologist after the results have been confirmed.
- Below $30.000/\mu\text{l}$: recheck the CBC and contact the haematologist immediately.
- When bleeding symptoms are present: contact the haematologist immediately for urgent referral or send the patient to the emergency unit.

FURTHER DIAGNOSTIC WORK UP AND VALUES FOR TREATMENT OF ITP

The further diagnostic work up for a suspected ITP has been well described in the publication of the practice guidelines by the BHS.¹⁴ These guidelines also set clear values for the initiation of treatment (Figure 4) and the therapeutic options. Active bleeding or platelet count below $10.000/\mu\text{l}$ make treatment mandatory. When there's no or mild bleeding and the platelet count is between 10 - $30.000/\mu\text{l}$, then treatment is

a potential option after evaluation of patient characteristics. When there's no bleeding and platelet count is above $30.000/\mu\text{l}$ then there's no need for treatment unless special circumstances are present (e.g. invasive procedure).

The decision to hospitalise a patient with ITP will be made by the haematologist primarily based on the haemorrhage situation (patients with signs of mucosal or deep bleeding are frequently admitted) and on factors influencing the bleeding risk (age, comorbidities, need for treatment with anticoagulant or antiplatelet agents, etc.).¹⁴

CONCLUSION

The use of alemtuzumab has been associated with the development of ITP in 2,6% of patients in clinical trials in MS. A lower frequency was reported in the post-marketing setting. Through the RMP, patients can be diagnosed early, and treated if needed, allowing for favourable outcomes. This important goal can be reached through a good education of the patient, a careful watch on the monthly lab tests and a close collaboration between the neurologist and the haematologist. The latter could be facilitated through the establishment of a reference network prior to initiation of alemtuzumab treatment. In this report, based on a consensus meeting with Belgian haematologists and neurologists, we have described different scenarios of platelet count abnormalities that can be encountered and the appropriate actions to take for every scenario.

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