REVOLADE (eltrombopag), thrombopoietin receptor agonist
Minor improvement in the treatment of acquired severe aplastic anaemia refractory and ineligible for stem-cell transplantation

Main points

- REVOLADE now has Marketing Authorisation in the treatment of adults with acquired severe aplastic anaemia who are either refractory to prior immunosuppressive therapy or heavily pretreated and who are ineligible for haematopoietic stem-cell transplantation.
- In the absence of survival data, this treatment is non-curative. It does nevertheless represent a minor improvement in treatment this new indication.

Pre-existing indications

REVOLADE also has Marketing Authorisation in the treatment of chronic autoimmune thrombocytopenic purpura and in the treatment of thrombocytopenia in association with chronic hepatitis C infection.

Therapeutic use

The management of acquired severe aplastic anaemia calls either for haematopoietic stem-cell transplantation or immunosuppressive therapy with antilymphocyte serum combined with cyclosporine, together with supportive care (transfusions of red blood cells and platelets, anti-infectious treatments). The choice between hematopoietic stem cell transplantation and intensive immunosuppressive therapy depends on the patient’s age and comorbidities and on the availability of a donor.

Apart from the indication for a stem-cell transplant, the reference treatment is based on a combination of antilymphocyte serum and cyclosporine. In the absence of response, a second treatment may be considered: with antilymphocyte serum and cyclosporine or transplantation of unrelated haematopoietic stem cells assuming a 10/10 phenoidentical donor is available.

Other treatments can also be used (without Marketing Authorisation) such as alemtuzumab, in particular in the case of major toxicity of cyclosporine and androgens.

Role of the medicinal product in the therapeutic strategy

In the case of acquired severe aplastic anaemia, REVOLADE is a non-curative treatment which has a place limited to adults either refractory to prior immunosuppressive therapy or heavily pretreated and ineligible for stem cell transplantation. In the absence of survival data, this medicinal product cannot lead to recovery since it neither follows the logic of a stem-cell transplantation, nor the induction of immunosuppression capable of removing the autoimmune “unmoved mover” of this condition.

REVOLADE should not be instituted in the presence of cytogenetic of chromosome 7 anomalies.

Clinical data

- The data in this new indication come from a non-comparative phase II study conducted in 43 patients with a mean age of 45.5 years and suffering from severe aplastic anaemia:
  - either regarded as refractory (i.e. with insufficient prior response to immunosuppressive therapy) in three-quarters of the cases (33/43):
  - or with an insufficient platelet response to prior treatments (10/43).

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On inclusion, the mean number of platelets was 20 G/L. Virtually all the patients had received transfusions of platelets (91%) and/or red blood cells (86%) in the month prior to inclusion. The preliminary data showed that among the 43 patients treated with REVOLADE, a haematological response to at least one of the three haematopoietic cell lines and/or a reduction in the need for transfusion (primary endpoint) was obtained, at 3 or 4 months, in 17 patients (40%) with an 8.9-month median duration of follow-up. This reduction in transfusional needs is likely to have an impact on the organisation of care. About one-half of the patients (22/43) stopped the treatment on account of inefficacy after 3 or 4 months of treatment.

- Treatment discontinuation due to adverse events was reported in 5 of the 43 patients (12%) treated with eltrombopag. The adverse events reported most often (>20%) were: nausea (33%), fatigue (30%), cough (23%), diarrhoea (21%) and headache (21%). One-third of the patients (14/43) presented at least one serious adverse event, primarily: febrile neutropenia (14%; 6/43), sepsis (5%; 2/43) and viral infections (5%; 2/43). Cytogenetic anomalies were detected in 8 (19%) of the 43 patients (including 5 chromosome 7 anomalies), with a median time to onset of 3.1 months. Owing to the slight regression and natural progression of the illness, there is some uncertainty concerning a potential association between the use of REVOLADE and the risk of the appearance of clonal cytogenetic anomalies or progression towards leukaemia or myelodysplastic syndrome in the more or less long-term.

- Overall, the efficacy and tolerability data for REVOLADE are limited and make it difficult to assess its therapeutic impact on the clinically relevant criteria such as quality of life, transfusional needs, hemorrhaging or infectious episodes. The long-term data, including those for survival and tolerability, are still limited (9 patients treated for over a year).

Special prescribing conditions

- Medicine for hospital prescription.
- This medicinal product is to be prescribed only by specialists in and departments of haematology, hepatology/gastroenterology, infectious diseases and internal medicine.

Benefit of the medicinal product

- The actual benefit* of REVOLADE is substantial.
- In view of:
  - the limited efficacy data,
  - uncertainties about its tolerability,
  - but considering the identified need in clinical practice at this infrequent and evolutionary stage of illness, REVOLADE provides minor clinical added value** (CAV IV) in its new indication.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

* The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means “no clinical added value”.

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