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LETTER TO THE EDITOR

Cardiac surveillance in the era of Duvyzat: do we need to do more?

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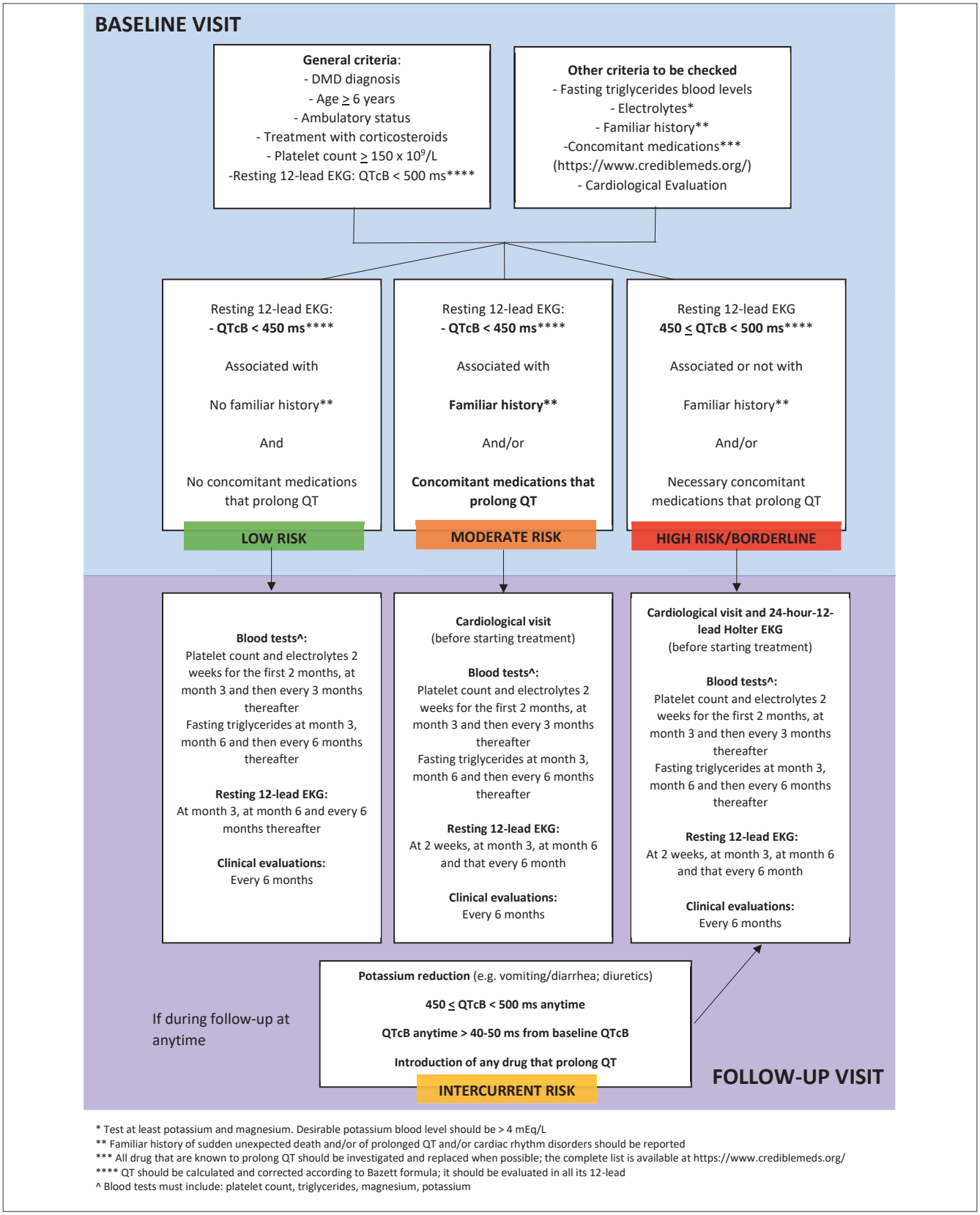
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Duchenne muscular dystrophy (DMD) is an X-linked recessive neurodegenerative disorder. In the last two decades, there have been several clinical trials with therapeutic approaches targeting different steps of the mechanisms underlying DMD[1]. One of these approaches uses Duvyzat (givinostat), a histone deacetylase inhibitor that has recently been approved for ambulant DMD boys aged ≥6 years, regardless of genetic mutation[2].

Since the drug became available in some countries, new safety data have become available mainly confirming the safety profile emerged from both phase 2 and 3 clinical trial[2]. The safety profile remained acceptable: platelet count reduction, diarrhea, and elevated triglycerides remain the major concerns, the first two primarily occurring in the first months and the increased triglycerides also in the second trimester after treatment is started.

More recently, following the availability in a much larger cohort in the real world, there has been some concern about the possible effect on the QT interval on EKG that had previously been found to be prolonged only in preclinical studies at much higher doses than those used in clinical practice. The QT interval had been thoroughly investigated in both clinical trials with no evidence of prolongation, but the question remains whether this holds true in a real world setting where other factors may contribute to produce an abnormal QT interval. As prolonged QT is a major cause of sudden death in young people, and DMD



* Test at least potassium and magnesium. Desirable potassium blood level should be > 4 mEq/L
** Familiar history of sudden unexpected death and/or of prolonged QT and/or cardiac rhythm disorders should be reported
*** All drug that are known to prolong QT should be investigated and replaced when possible; the complete list is available at https://www.crediblemeds.org/
**** QT should be calculated and corrected according to Bazett formula; it should be evaluated in all its 12-lead
^ Blood tests must include: platelet count, triglycerides, magnesium, potassium

Figure 1. Suggested surveillance flow-chart.

in itself implies an increased risk of malignant cardiac arrhythmias compared to the general population, maintaining a close surveillance on this aspect is paramount.

This information has led to a discussion in the clinical community of whether a more accurate surveillance should be used. In Italy, a panel of clinical experts in DMD organized several meetings also involving cardiologists with specific expertise in the study of the QT interval in order to identify possible other factors that may contribute to prolong the QT. Several elements that until now have not been systematically explored, have been now identified. These include QT baseline values below 500 ms but above 450 ms, a difference of 40-50ms from baseline EKG, subclinical low potassium blood level (< 4 mEq/L), family history of sudden unexpected death, and the presence of concomitant medications known to prolong QT (https://www.crediblemeds.org) [3] that may already be taken on a regular basis at the time therapy with Duvyzat is started (e.g., some antipsychotics) or may be administered following intercurrent episodes (e.g., some antibiotics) [3]. This is of particular importance in these boys who are prone to develop respiratory events that may need antibiotics [4] and, because of the known effect of dystrophin on brain, there is an increasing number of patients treated for behavioral or psychiatric problems [5]there has been increasing attention to the involvement of the central nervous system in Duchenne muscular dystrophy (DMD).

According to the label, Duvyzat can be administered in ambulant DMD boys older than 6 years who are already receiving steroid treatment and have platelet count > 150x 10^9 and QT interval < 500 ms. The suggestion from our group, in agreement with specialist cardiologists was that it could be useful to collect additional information at baseline that would allow to better understand the risk of developing prolongation of QT interval irrespective of Duvyzat. These would allow us to identify different groups based on a low-, moderate- or high-risk of developing prolonged QT intervals. Based on these criteria, the follow-up after baseline should be shaped accordingly (Fig. 1).

Particular attention was also paid to the possibility that these events may occur at any time during long-term therapy, in relation to intercurrent episodes that may cause potassium reduction (e.g., vomiting) or to the introduction of any drug that may prolong QT.

Because of this, there was a suggestion that a 24-hour-12-lead Holter EKG should be repeated in the presence of these events to evaluate the possible impact on the QT.

While there is no evidence from real-world data that Duvyzat may affect QT, we suggest that at the time the drug will be given at a rapidly increasing number of DMD individuals worldwide more attention should be paid to identify possible concomitant risk factors. A more detailed monitoring plan, as suggested in this letter, may help to obtain a more precise profile of the possible occurrence and severity of QT prolongation in individuals receiving Duvyzat over long-term treatment courses.

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