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BRIEF COMMUNICATION

A Small Change Can Make a Big Difference: A Lesson from Evolocumab

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Background Evolocumab is an expensive proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor which has been shown to significantly improve cardiovascular outcomes in high risk patients.

Methods This is a case study describing a stepwise approach to ''PCSK9 inhibitor non-response" in a patient with familial hypercholesterolaemia. There are a few described pathophysiological mechanisms for ''PCSK9 inhibitor non-response" including homozygous LDL-C receptor-negative mutations and alteration in the binding site of PCSK9 inhibitors.

Results We report the case of a 41-year-old woman with familial hypercholesterolaemia and premature cardiovascular disease, who was non-responsive to the action of PCSK9 inhibitor solely due to the incorrect subcutaneous injection technique.

Conclusions This case study highlights the importance of reviewing the accuracy of SC injection technique in patients with minimal or no response to PCSK9 inhibitors prior to proceeding to costly genetic testing.

Keywords Evolocumab • PCSK9 inhibitor • Familial hypercholesterolaemia • Coronary artery disease

Background

Familial hypercholesterolaemia (FH) is a common monogenic lipid disorder characterised by elevated plasma low-density lipoprotein cholesterol (LDL-C). Patients with FH are at significantly elevated risk for early onset cardiovascular events and death from coronary heart disease [1].

Evolocumab is a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor that binds to serum PCSK9 and slows down LDL-C receptor degradation resulting in lowering of circulating LDL-C [2]. Evolocumab is currently available in Australia on the Pharmaceutical Benefit Scheme for patients with FH diagnosed by the Dutch Lipid Clinical Network Criteria (DLCNC). The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial studied the cardiovascular outcomes in patients at high risk for cardiovascular disease taking evolocumab on a background of statin therapy and showed a significant improvement in cardiovascular events [3].

Evolocumab is an expensive medication, and the clinical cost effectiveness of PCSK9 inhibitors has been under scrutiny from a public health perspective. Several authors have suggested that the best approach to delivering the potential health benefits of PCSK9 inhibitors therapy at a reasonable cost is by reducing the price of the drug [4]. Furthermore, selection of high risk patients, adequate education and clinical vigilance should be at the cornerstone of PCSK9 inhibitor administration.

Formerly, a subgroup of patients with genetic mutations described as ''PCSK9 inhibitor non-responsive", including homozygous receptor negative mutations resulting in LDL-C receptor inactivity, and an alteration in the PCSK9 binding site, have been postulated as other mechanisms of non-responsiveness [5].

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Case

A 41-year-old woman was admitted to hospital with acute anterior ST elevation myocardial infarction in January 2017 when she was also diagnosed with FH. Her initial biochemistry tests revealed TC = 10.1, LDL-C = 8.2, TG = 1.9 and HDL = 1.1 mmol/L. She also reported a strong family history of premature coronary artery disease and elevated serum cholesterol in her first degree relatives. Her other cardiovascular risk factors included hypertension and smoking. Physical examination revealed bilateral arcus cornealis and Achilles tendon xanthoma confirming a phenotypic diagnosis of FH with DLCNC of 14. Her condition became complicated by ischaemic cardiomyopathy with reduced left ventricular ejection fraction of 35%, assessed by transthoracic echocardiogram. She received daily atorvastatin 80 mg and ezetimibe 10 mg as initial LDL-C lowering agents.

Two months later her LDL-C level had reduced to 5 mmol/L in conjunction with diet and lifestyle modification. Subsequently, she was commenced on evolocumab subcutaneous injections of 140 mg every fortnight. Eight weeks later, the LDL-C level was similar at 4.7 mmol/L, despite having received four injections of evolocumab.

In the first instance, the injection technique was reviewed and was found to be incorrect. Several errors were observed while she was demonstrating the technique by an injection simulator: firstly a ''stretch method'' was used on the abdominal site (instead of the preferred ''pinch method''); secondly, the selected region of skin comprised of hard consolidation (likely thickened subcutaneous fat); finally low pressure was applied over the skin and perhaps this led to either an intradermal injection or into an area with substantial thickened subcutaneous fat. As a result, there was minimal or no distribution of the medication into the subcutaneous tissue. The injection technique was rectified and evolocumab therapy was continued under the supervision of a medical practitioner. Six weeks later lipid profile showed a marked improvement with TC = 2.5, LDL-C = 1.0, TG = 1.0 and HDL = 1.1 mmol/L. This case highlights that a faulty injection technique due to intradermal rather than subcutaneous injection, as well as injecting to an area with thickened subcutaneous fat, resulted in suboptimal absorption and consequently ''PCSK9 inhibitor non response''. If not recognised, this could lead clinicians towards costly genetic testing to search for rare gene mutations.

Discussion

Evolocumab for subcutaneous administration is supplied in a single-use prefilled auto-injector containing 140 mg in 1 ml of solution. It is recommended that this should be injected by a well-trained individual until the patient becomes comfortable and skilled to perform self-injection. The injection should be administered in rotating sites over the abdomen (except for a two-inch area around navel), thigh and outer area of upper arm. The auto-injector should be held perpendicular (90°) to the stretched or pinched skin, depending on site of injection (''pinch method'' preferred for abdominal site and ''stretch method'' for thigh and upper arm). Subsequently, it needs to be firmly pushed onto the skin until it stops moving. Finally, the start button is pressed held for 15 seconds until injection is completed.

Furthermore, perfusion characteristics of the tissue, namely functional capillary density, is an important element in the effectiveness of subcutaneous medications [6]. Although there are only limited data about factors which may potentially interfere with delivering of evolocumab from subcutaneous tissue, the injection should be avoided into areas of skin which are hard, thickened, bruised, red, tender or over a tattoo as the histology of the region may have been altered [7].

Conclusion

PCSK9 inhibitors are an expensive but effective treatment for patients with FH at elevated cardiovascular risk. This case demonstrates that faulty injection technique is a potential cause of ''PCSK9 inhibitor non-response'' which can simply be managed by adequate education.

- Evolocumab, a PCSK9 inhibitor, is an effective lipid lowering agent in patients with familial hypercholesterolaemia
- Clinical vigilance for non-responsiveness to PCSK9 inhibitors is required
- A simple faulty injection technique can lead to PCSK9 inhibitor non-response
- Other causes of PCSK9 inhibitors non-response include genetic mutations and immunogenicity.

Conflict of Interest

SM has received honorarium and study grant from Amgen.

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