

Title Page

Title: Drug induced vitiligo-like depigmentation from a CDK 4/6 inhibitor

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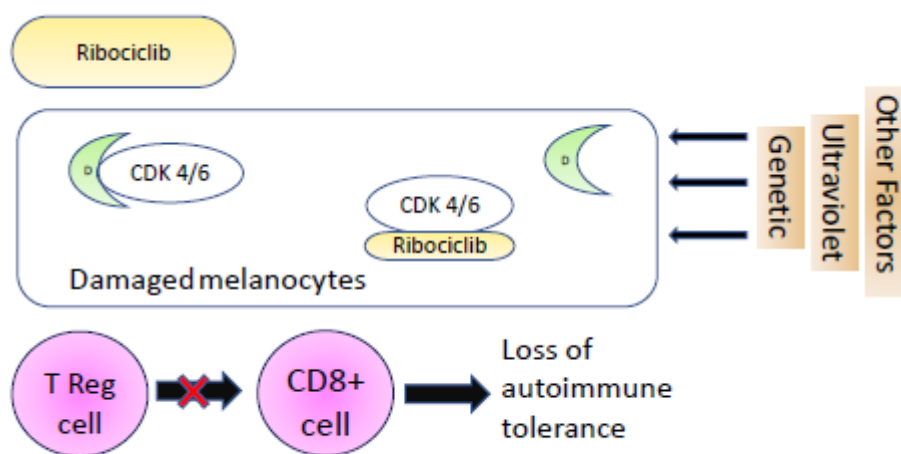
Abstract:

Ribociclib is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK 4/6) that is used in combination with an aromatase inhibitor in the first-line setting for advanced or metastatic hormone receptor positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer. We report two cases of drug-induced vitiligo-like depigmentation (DI-VLD) associated with ribociclib. The awareness of this side effect is important given the increasing use of this drug and others with a similar mechanism of action.

Keywords: drug adverse reaction, vitiligo, ribociclib, CDK4/6 inhibitors

Graphical Abstract Text:

Ribociclib is used in combination with an aromatase inhibitor to treat metastatic breast cancer. We report two cases of drug-induced vitiligo-like depigmentation (DI-VLD) associated with ribociclib. The awareness of this side effect is important given the increasing use of this drug and others with a similar mechanism of action.



1. The proposed mechanism behind DI-VLD from CDK4/6 inhibitors.

Ribociclib is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK 4/6) that is used in combination with an aromatase inhibitor in the first-line setting for advanced or metastatic hormone receptor positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer.(1) We report two cases of drug-induced vitiligo-like depigmentation (DI-VLD) associated with ribociclib.

Case 1 is a 71-year-old Caucasian female treated with ribociclib (600 mg daily for 21 days followed by 7-day rest initially, reduced to 400 mg after 4-week due to neutropenia) and letrozole for metastatic breast cancer. Grade one skin depigmentation on lower legs started after 28 weeks of treatment and progressed to grade two after 32 weeks of treatment, involving sun exposed areas of legs, arms, V of neck, cheeks, posterior neck, and back (Figures 1&2). The depigmentation remained at the same level until ribociclib cessation,

after a further 8 months, due to disease progression. At the 12 month post-treatment follow up, there was no evidence of repigmentation. Concomitant medications included omeprazole, olmesartan, and amlodipine. Past medical history included right-sided mastectomy for an invasive ductal breast carcinoma and left-sided mastectomy for a lobular breast carcinoma.

Case 2 is a 54-year-old Indian female with metastatic breast cancer treated with ribociclib (600mg on above schedule) and letrozole. Grade one skin depigmentation involving her face, arms and trunk occurred after 11.5-weeks of treatment. Concomitant medications included denosumab, paracetamol and oxycodone. The depigmentation progressed after 31 weeks to grade two, remaining at this level until ribociclib cessation, after a further 28 months, due to disease progression. The total surface area of depigmentation lessened over several months but some remain over her arms and upper chest. Past medical history included left breast ductal-lobular carcinoma. Both cases did not report personal or familial history of autoimmunity.

Ribociclib targets the cyclin-D-CDK4/6-P6-retinoblastoma pathway that is often disrupted in cancer cells leading to disinhibited growth. (2) In the first-line trial of ribociclib and letrozole, 22% (74/334) developed cutaneous adverse events (AEs) and of these, 1.5% were grade three AE and none were grade four.(1) Two other CDK4/6 inhibitors, palbociclib and abemaciclib, reported similar incidence of cutaneous AEs.(3)(4) To our knowledge, no DI-VLD associated with CDK4/6 inhibitors have been reported so far.

Letrozole, an aromatase inhibitor (AI), has been used for twenty years without reported association with vitiligo(5) although subacute cutaneous lupus erythematosus, rheumatoid arthritis and altered markers of innate, adaptive, and NK-cell-related immunity are described following AIs.(6) A modulating effect of letrozole in VLD cannot be excluded

in our cases, but a primary role is unlikely. The other co-medications are similarly unlikely causes given their well-established usage without described association with vitiligo. By contrast, the temporal relationship between depigmentation and ribociclib exposure, the rapid evolution of depigmentation, and stabilization after therapy cessation in our cases suggest ribociclib as the cause of VLD.(7)

The pathogenesis of DI-VLD and its relationship to vitiligo is unclear. Vitiligo pathogenesis involves intrinsic defects with melanocytes which lead to the loss of immune tolerance to these cells. DI-VLD is uncommon, except in metastatic melanoma patients receiving immune checkpoint inhibitors and can affect up to 25% of patients during treatment.(8) Study of this group of patients has improved the understanding of DI-VLD. However, it remains unclear whether DI-VLD shares a similar pathogenesis to vitiligo. (9) Factors apart from the cancer and the medication are likely required for DI-VLD to occur given its infrequent observation in the pivotal ribociclib trials. These factors are not completely understood but hypothesised to include genetics and environmental triggers. High level of ultraviolet radiation (UVR) is common in Australia and may be a trigger for DI-VLD. Sun damaged melanocytes may be targeted by an augmented immune system following CDK 4/6 inhibition, due to loss of immune tolerance resulting from reduction of immunosuppressive regulatory T-cells and enhanced activation of cytotoxic T-cells.(10) (UVR can also inhibit CDK 4/6 via p16 induction, but the relevance of this is unknown.) DI-VLD could be a class effect from the CDK 4/6 inhibitors as the proposed mechanism is not limited to ribociclib. There are no similar cases reported in the literature to date, which may be due to a lack of recognition, underreporting or the infrequency of DI-VLD in clinical practice.

CDK 4/6 inhibitor induction of depigmentation (and potential associations with UVR, koebnerisation, secondary generalization and other autoimmunity) may vary with the particularities of both the drug and the tumour. As the use of CDK 4/6 inhibitors is increasing with the possibility of their use in the adjuvant setting, more data will help the understanding and management of DI-VLD.

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Figure 1a and b). DI-VLD of the upper limbs.

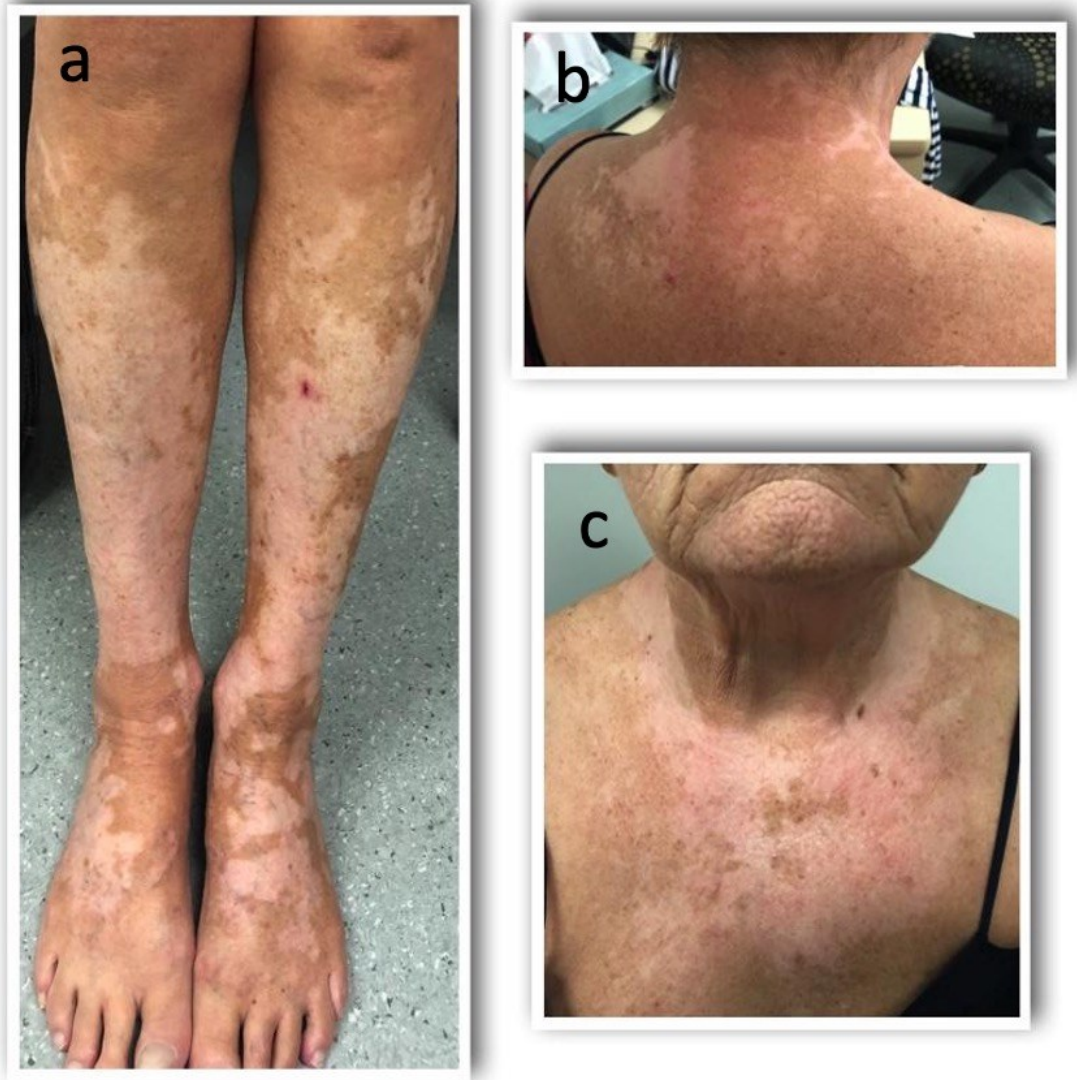


Figure 2a). DI-VLD of the lower limbs 2b). Upper back 2c). V of neck depigmentation mainly affecting sun exposed areas.