Beneficial effect of ustekinumab in familial pityriasis rubra pilaris with a new missense mutation in CARD14

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Summary

Pityriasis rubra pilaris (PRP) represents a group of rare chronic inflammatory skin disorders in which around one in 20 affected individuals show autosomal dominant inheritance. In such cases there may be gain-of-function mutations in CARD14, encoding caspase recruitment domain-containing protein 14 (CARD14), which activates the noncanonical nuclear factor (NF)-κB pathway, thereby promoting cutaneous inflammation. Here we report a mother and son with PRP due to a new missense mutation in CARD14 and describe the beneficial clinical effects of ustekinumab, a monoclonal antibody against interleukins 12 and 23, in both patients. A 49-year-old woman and her 20-year-old son had lifelong, generalized, patchy erythematous scale with a few islands of sparing, as well as minor nail ridging and mild palmoplantar keratoderma, features consistent with generalized PRP. Topical steroids, phototherapy and oral retinoids proved ineffective. Following informed consent, Sanger sequencing of CARD14 in both individuals revealed a new heterozygous single-nucleotide transversion in exon 4, c.356T>G, resulting in the missense mutation p.Met119Arg. Ustekinumab, at a dose of 45 mg every 12 weeks, brought about a significant physical and emotional improvement in both the mother and son within a few days of the initial dose, which was sustained on maintenance dosing. This report highlights the therapeutic potential of biologics that downregulate NF-κB signalling in familial PRP with mutations in CARD14.

What’s already known about this topic?

- Pityriasis rubra pilaris (PRP) represents a group of rare chronic inflammatory skin disorders in which some cases show autosomal dominant inheritance.
- Some cases also reveal heterozygous gain-of-function mutations in CARD14, encoding caspase recruitment domain-containing protein 14 (CARD14).
- Ustekinumab, an interleukin-12/23 antagonist, is a licensed biological therapy for psoriasis, although its use has not been widely assessed in PRP, despite anecdotal reports of its potential efficacy.

What does this study add?

- We report a mother and son with refractory generalized PRP. DNA sequencing revealed that both carried a new de novo missense mutation in CARD14, p.Met119Arg.
- Identification of this CARD14 mutation was used as justification for a trial of ustekinumab, wherein both patients had a beneficial clinical response, physically and emotionally, with sustained improvements over several months of follow-up.
- Ustekinumab may be considered as a targeted anti-inflammatory therapy for familial PRP with an underlying mutation in CARD14.
Pityriasis rubra pilaris (PRP) represents a group of rare chronic inflammatory skin disorders, which may show clinicopathological overlap with psoriasis. Most cases of PRP are sporadic, but around one in 20 show autosomal dominant inheritance. Moreover, some cases of familial PRP have been shown to result from gain-of-function mutations in CARD14.

**Fig 1.** Pedigree, molecular pathology and clinical features of the mother and son with autosomal dominant pityriasis rubra pilaris. (a) Pedigree: Sanger sequencing of CARD14 was performed in all family members (affected and unaffected) shown in this autosomal dominant pedigree (mother is indicated by arrow). (b) Heterozygous missense mutation (c.356T>G; p.Met119Arg) in CARD14, which was present in the affected mother and son but not in any of the other unaffected family members. (c) Clinical responses at baseline and after 12 weeks of therapy with ustekinumab in the mother and son.
encoding caspase recruitment domain-containing protein 14 (CARD14).\(^1\) CARD14, also known as CARD-containing membrane-associated guanylate kinase (MAGUK) protein 2 (Carma 2), is a member of a family of scaffold proteins involved in cell adhesion, signal transduction and cell polarity control.\(^6\) CARD14 binds to B-cell lymphoma 10 through a CARD–CARD interaction and activates the noncanonical nuclear factor-kB pathway, thus promoting inflammation.\(^4\) The significance of CARD14 mutations in PRP may also extend to therapy, as a few previous reports have highlighted good clinical responses to biologics, such as ustekinumab, when conventional anti-inflammatory therapies have not led to patient benefit.\(^5\)–\(^8\) However, in all the reports the benefit of ustekinumab was demonstrated in only one case with a known CARD14 mutation.\(^8\) In this report we describe a mother and son with generalized PRP, identify a new CARD14 mutation and demonstrate major physical and emotional improvements following treatment with ustekinumab.

Case report

A 49-year-old woman presented with widespread erythema and scale. Her skin had been normal at birth, but around age 6 weeks she developed erythematous patches on both cheeks followed by more generalized dry red scales with peeling that persisted into adulthood. Examination revealed generalized, confluent erythematous scale affecting the face, body and limbs, and a few islands of spared, apparently unaffected skin. She had minor nail ridging and mild palmoplantar keratoderma. Her 20-year-old son had a similar clinical course that began in his first few weeks of life, although his skin developed more patchy, serpiginous, dry and thick scale with associated erythema. A clinical diagnosis of autosomal dominant familial PRP was made. The pedigree is shown in Figure 1(a).

Treatment with oral retinoids, phototherapy and topical steroids proved ineffective in both patients. Following informed consent, Sanger sequencing of CARD14 using peripheral blood DNA as a template was performed on the affected members and all unaffected members of the family. This revealed a heterozygous single-nucleotide transversion c.356T\(\rightarrow\)G in exon 4, which converts methionine (ATG) to arginine (AGG), designated p.Met119Arg (Fig. 1b). This missense mutation was detected in both the affected mother and her son but not in other unaffected relatives or in > 120 000 control alleles (http://exac.broadinstitute.org/). This amino acid substitution is located adjacent to other gain-of-function mutations between the CARD and coiled-coil domains.\(^1\)\(^,\)\(^9\) The functional effect of this missense mutation, assessed with various programs,\(^1\)\(^0\)–\(^1\)\(^4\) strongly indicates its pathogenic potential and that p.Met119Arg is a pathovariant variant (SIFT: 0.107, tolerated; PolyPhen-2: 0.244, benign; MutationTaster: 0.999, disease causing; CADD: 23.9, damaging; DANN: 0.964, pathogenic).

Both mother (weight 66 kg) and son (weight 65 kg) were treated with subcutaneous ustekinumab 45 mg every 12 weeks after two loading doses at weeks 0 and 4. Both Psoriasis Area and Severity Index (PASI), adopted as a measure of disease severity for PRP, and Dermatology Life Quality Index (DLQI) were assessed for the mother and son at baseline and 12 weeks and 24 weeks after the initiation of ustekinumab. At baseline, the mother had a PASI of 25.7 and DLQI 18, and the son had a PASI of 29.2 and DLQI 22. A dramatic clinical improvement was observed within a few days of the initial loading dose and was clearly evident after 12 weeks, with corresponding PASI < 1 and DLQI 0 for the mother, and PASI 4.8 and DLQI 3 for the son (Fig. 1c), which persisted for a total of 24 weeks. However, the clinical benefit in the mother waned around 30 weeks after initiation, but the skin improved again after the dose of ustekinumab was increased from 45 mg to 90 mg every 12 weeks.

Approximately 12 weeks after the ustekinumab dose increase, the mother had normal fingernails for the first time in her life. Both individuals have been observed for > 8 months on treatment and the improvement has been maintained. For individuals with psoriasis, an HLA-Cw6 genotype has been associated with an improved response to ustekinumab, but genotyping in both the mother and son with PRP (using published methods)\(^1\)\(^5\) revealed that they were both HLA-Cw6 negative. There were noticeable personal benefits for both individuals, due to improved physical and emotional well-being, following the improvement with ustekinumab after many years of impaired quality of life due to PRP. Details of the positive impact that ustekinumab had on the mother’s life are recorded in her own words in Appendix S1 (see Supporting Information).

In summary, the positive response to treatment with ustekinumab in both the mother and son highlights the efficacy of this biological therapy in PRP, with the discovery of an underlying mutation in CARD14 being the driver towards pursuing this particular targeted anti-inflammatory therapy.

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References


Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Appendix S1 A personal account by the mother with familial pityriasis rubra pilaris on ‘how ustekinumab has changed her life’.