Overall, GTN patches were effective in 55% of the treated patients. Efficacy was better than that of nifedipine and amlodipine (33 vs 25% response rate, respectively), but small numbers and retrospective analysis does not allow statistical comparison. Response was similar in primary and secondary RP. Children with severe RP had a better response to nifedipine and amlodipine than children with moderate disease. The sub-group with severe disease was more likely to be using a disease-modifying drug, which may have had an impact. However, numbers are too small for any conclusion to be drawn from this.

Application of GTN patches allows removal if adverse events occur. Together with absence of tablets, this may make treatment with GTN attractive in paediatric practice. All patients received Deponit GTN patches. Alternative brands may not have adequate skin adhesion when cut into quarters for this off-license use.

GTN patches, nifedipine and amlodipine offer symptomatic relief for patients with moderate primary/secondary RP. Further studies, including head-to-head trials, are needed to determine if one agent is superior. Meanwhile, GTN patches offer an alternative to oral calcium channel blockers for symptomatic relief of paediatric RP.

References


**Table 2** Details of response to sequential treatments where applicable (n = 10)

<table>
<thead>
<tr>
<th>No.</th>
<th>Severity of disease</th>
<th>First treatment</th>
<th>Second treatment</th>
<th>Third treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Severe</td>
<td>Amlodopine</td>
<td>Nifedipine</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>Amlodopine</td>
<td>GTN</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Amlodopine</td>
<td>GTN</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>Nifedipine</td>
<td>Amlodipine</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>Severe</td>
<td>Nifedipine</td>
<td>Nifedipine</td>
<td>GTN</td>
</tr>
<tr>
<td>6</td>
<td>Moderate</td>
<td>Nifedipine</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>Severe</td>
<td>GTN</td>
<td>Nifedipine</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>Moderate</td>
<td>Nifedipine</td>
<td>GTN</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>Severe</td>
<td>Amlodopine</td>
<td>Nifedipine</td>
<td>GTN</td>
</tr>
<tr>
<td>10</td>
<td>Moderate</td>
<td>Amlodopine</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*: no response/adequate response; √: response.

Rheumatology key message

- GTN patches are an efficacious treatment option in paediatric RP.

Disclosure statement: The authors have declared no conflicts of interest.

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A case of early-onset sarcoidosis with a six-base deletion in the NOD2 gene

Six, we present the first case of early-onset sarcoidosis (EOS, MIM no. 609464) with a six-base deletion in the NOD2 gene, resulting in the replacement of one amino acid and the deletion of two additional amino acids. All previous mutations reported for EOS and Blau syndrome (BS, MIM no. 186580) were single-base substitutions that resulted in the replacement of a single amino acid [1–3].

The patient was a Japanese male born after an uncomplicated pregnancy and delivery. His family had no symptoms of skin lesions, arthritis or uveitis. At 5 years of age, he was diagnosed with bilateral severe uveitis. He became blind in both eyes during adolescence. He had swollen ankles without pain during childhood.
and developed arthritis in his both knees and ankles at 15 years of age. At 30 years, a skin rash had developed on his extremities after his first BCG vaccination. The skin lesions were scaly erythematous plaques with multiple lichenoid papules and some pigmentation. At the same age, camptodactyly without obvious synovial cysts of the hands was observed, and the deformity in all fingers developed by 35 years. At 41 years, he had low-grade fever for 1 year. He had no pulmonary lesions. His laboratory investigations showed normal white blood cell count, mildly elevated CRP (1.0 mg/dl) and ESR (20 mm/h). A skin biopsy from his left forearm revealed non-caseating granulomas without lymphocyte infiltration. There were no indications of infection by Mycobacterium.

The clinical symptoms and pathological findings on the biopsied skin indicated that the patient suffered from EOS. It has been reported that EOS and BS have a common genetic aetiology due to mutations in the NOD2 gene that cause constitutive Nuclear Factor (NF)-κB activation [4, 5]. Thus we analysed the NOD2 gene from the patient to look for mutations that might correlate with the pathology of EOS. A written informed consent was obtained from the patient and his families, according to the protocol of the institutional review board of Kyoto University Hospital and in accordance with the Declaration of Helsinki. Genomic sequencing analysis of the patient’s NOD2 gene showed the presence of a heterozygous deletion of six bases in exon 4, which resulted in c.1493_1498delAACTGT, p.E498V, 499–500del (Fig. 1A). The mutation was novel and was not identified in 100 normal controls. A genome alignment of NOD2 among several species showed that E498, L499 and L500 are conserved from zebrafish to human (Fig. 1B). These data strongly suggested that the identified deletion of six bases in the NOD2 gene is not a single nucleotide polymorphism (SNP), but is probably responsible for EOS in the patient.

Previous studies report that NOD2 mutations causing EOS/BS show constitutive activation of NF-κB [6–8]. Therefore, we investigated the level of NF-κB activity associated with the new mutation identified here. First, we confirmed the level of mRNA expression of the mutated allele by subcloning analysis of NOD2-cDNA, which showed that the mutated allele was expressed as well as the wild type allele (data not shown). We then evaluated the ability of the NOD2 mutant to constitutively activate NF-κB by using an in vitro reporter system in HEK293T cells transfected with both NOD2 mutants and NF-κB reporter plasmids (Fig. 1C). The deletion mutant demonstrated almost five times more NF-κB activity than wild type without muramyl dipeptide (MDP) stimulation. Western blot analysis confirmed that NOD2 mutant protein expression was similar to that of wild type (Fig. 1C). Thus, like other mutations of NOD2 identified previously, the deletion mutant identified here also showed constitutive activation of NF-κB.

The mechanism underlying EOS/BS has not been totally understood, although two pathways downstream from NOD2 have been identified: NF-κB activation through receptor-interacting protein (RIP) like interacting caspase-like apoptosis regulatory protein kinase (RICK) and MAP kinase activation through the caspase recruitment domain 9 (CARD9) [9]. We previously tested 10 NOD2 missense mutations that have been identified in our cohort of EOS/BS patients in Japan, and all of them demonstrated constitutive activation of NF-κB [3]. By analysing this newly identified deletion mutant, we have further confirmed the importance of constitutive activation of NF-κB by mutated NOD2 for the pathogenesis of EOS/BS. We would like to emphasize the
usefulness of the NF-κB reporter assay with mutant NOD2 for observing its role in EOS/BS, although the MAP kinase activation pathway and other possible pathways need to be evaluated to more completely understand the pathogenesis of the NOD2 mutation in EOS/BS.

We have identified the first deletion mutation in the NOD2 gene responsible for EOS/BS, and the mutant showed constitutive activation of NF-κB, which is one of the key features that lead to the pathogenesis of EOS/BS.

Rheumatology key message

- A six-base deletion in NOD2 gene causes EOS.

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