rapid disease progression and evidence of increased interferon pathway activation, we initiated off-label oral treatment with baricitinib (initial dose 0·025 mg/kg per day [0·5 mg/day]). We increased baricitinib weekly by 0·5 mg/day, up to 0·4 mg/kg per day (8 mg/day in four single doses). In view of the clinical and laboratory similarities between interferonopathies and the condition of our patient, we chose the Janus kinase 1/2 inhibitor baricitinib because of its beneficial effects in interferonopathies.[3,4] This treatment led to clinical stabilisation after a few weeks, disappearance of the skin lesions, and stabilisation of MRI findings (figure 1). However, after 8 months, partial progression occurred when the patient developed increased weakness of her head and trunk muscles. We added oral hydroxychloroquine (4 mg/kg per day [100 mg/day]; figure 2F), which was discontinued after 4 months because of disease progression. After hydroxychloroquine was discontinued, we added low-dose cyclophosphamide (25 mg/m^2 per day), which we discontinued after 4 months due to disease progression and sleepiness. We then started off-label therapy with the monoclonal IFNAR1 inhibitor anifrolumab, which has been developed for (but not yet approved in) adults with systemic lupus erythematosus.[5] Because no data are available on the dosage of anifrolumab in children (in adults, dosage is 300 mg intravenously every 4 weeks), we initiated treatment with 200 mg every 4 weeks. However, after the third 200 mg dose, we reduced the dose to 150 mg because the patient had pneumonia requiring hospitalisation. The patient had a spontaneously resolved episode of fever and increased C-reactive protein, without identification of a cause, 3 days after the fourth 150 mg dose of anifrolumab. Co-treatment with baricitinib and anifrolumab resulted in a rapid clinical, radiological, and laboratory improvement, with better cognitive abilities and muscle strength.

The patient's interferon score and CD169 expression on monocytes normalised after baricitinib initiation, increased under co-medication with cyclophosphamide, and decreased again after cyclophosphamide was stopped. Interferon scores were lowest under co-medication with baricitinib and anifrolumab (figure 2F).[6]

In conclusion, this case underlines the contribution of type I interferon signalling to malignant atrophic papulosis with CNS involvement and provides evidence that the disease can be caused by a gain-of-function *IFNAR1* variant. Treatment with baricitinib and anifrolumab effectively slowed disease progression. A randomised controlled trial of baricitinib or anifrolumab, or a combination, in genotyped patients with malignant atrophic papulosis might be warranted.

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Time to revise primary prevention guidelines for stroke and cardiovascular disease

Strategies for prevention of cardiovascular disease that are based on risk assessment and targeted to high-risk populations (ie, the so-called high-risk approach) are thought to deliver large benefits and to be cost-effective, compared with population-wide strategies.[1] According to this high-risk approach, management guidelines for blood pressure and cholesterol must be based on the use of an individual's predicted absolute risk of cardiovascular disease as the threshold for drug therapy. However,

evidence supporting the efficacy and cost-effectiveness of risk-based management guidelines (including risk-stratified heat maps) is scarce, and the global burden of stroke and cardiovascular disease continues to rise.

At a population level, age-standardised incidence and mortality rates of stroke and cardiovascular disease were decreasing long before the implementation of high-risk strategies. After the introduction of high-risk strategies into clinical practice over the past several decades, the decreases in incidence and mortality were expected to continue and even accelerate. However, between 2010 and 2015, decreasing rates of age-standardised mortality started to plateau across most regions[2] and subsequently started to increase, most notably in people younger than 70 years. For example, the age-standardised incidence of stroke and cardiovascular disease increased from 682 cases per 100 000 people (95% uncertainty interval 645–722) in 2017 to 684 cases per 100 000 people (646–726) in 2019, and stroke incidence increased from 149 cases per 100 000 people (136–166) in 2017 to 151 cases 100 000 people (137–167) in 2019. Furthermore, evidence shows that the prevalence of diabetes, arterial hypertension, and obesity is increasing, with greater relative increases in younger individuals (aged 30–59 years) than in older people (aged ≥60 years).[3] These findings suggest that primary prevention by means of high-risk strategies is not sufficiently effective at the population level for containing, let alone reducing, the rising global burden.

The high-risk prevention strategy is not only inadequate, but it might also exacerbate socioeconomic inequalities, provide a false reassurance for individuals at low and moderate risk that they are protected from stroke and heart attack, and attenuate any motivation to control their risk factors.[4] Additionally, the high-risk strategy can only prevent a few stroke and cardiovascular events, because it targets only a minority of the population at high risk.[4]

Findings from two large individual-participant meta-analyses[5,6] have convincingly shown that lowering blood pressure and plasma lipid concentration was beneficial, irrespective of the baseline measurements of these risk factors. An individual-participant meta-analysis[5] of 358 707 participants from 51 randomised controlled trials conducted by the Blood Pressure Lowering Treatment Trialists' Collaboration showed a beneficial effect of a pharmacological reduction in blood pressure to 120/70 mm Hg in people across various age groups (aged <55 years to ≥85 years), with relative risk reductions for prevention of major events (including stroke and heart attack) irrespective of baseline systolic or diastolic blood pressure. These findings were in line with the results of another individual-participant meta-analysis[6] of 18 162 participants from three trials of fixed-dose combination treatments (ie, two agents that lowered blood pressure plus a statin with or without aspirin) for primary prevention, which also reported a strong beneficial effect of lowering blood pressure and lipid concentration through pharmacological therapy regardless of baseline blood pressure and plasma lipid concentration. These results support a population-wide approach to lowering blood pressure and cholesterol, irrespective of baseline blood pressure and cholesterol concentration, and of absolute risk. This approach can be implemented by non-pharmacological interventions, such as public-health policy and individual lifestyle modification.

Considering this evidence, the World Stroke Organization and the World Federation of Neurology state that treatment thresholds for absolute risk should not be the main and only criteria for selecting individuals for pharmacological management of elevated blood pressure and lipid concentration. We also propose that the categorisation of people into low, moderate (mild), and high absolute cardiovascular risk (including use of risk-stratified heat maps) should be abandoned. More effective and widely applicable motivational preventative strategies, with emphasis on lifestyle modification, should be implemented for people at any risk of stroke and cardiovascular disease.

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