

## letters

### Recalcitrant psoriasis responding to new biologic drug: Ustekinumab

**To the Editor:** Psoriasis is a chronic inflammatory skin disease affecting 2% of the population.<sup>1</sup> This disease affects the skin and is associated with significant patient morbidity. Conventional topical and systemic treatment options are numerous with varying degrees of success and rapidity of action. The immunological pathogenesis of this condition has substantially grown in the recent years. All the advances have led to the development of biologic agents that have dramatically altered the treatment of moderate-to-severe psoriasis. Most of these agents are tumor necrosis factor (TNF) alpha-blockers, such as etanercept, infliximab, and adalimumab, which have shown a notable efficacy in the treatment of this condition. A new class of biologic agent ustekinumab, an interleukin (IL)-12 and IL-23 antibody, has shown a significant improvement when treating psoriasis, without the safety concerns, such as risk of infections associated to the former biologic agents. We present a case of a patient with severe plaque psoriasis refractory to multiple therapies, with a good response to ustekinumab.

A 56-year-old male presented to our hospital with recalcitrant plaque psoriasis for the last 40 years. The previous medical history showed smoking (1 pack per day), hypertension treated with enalapril 50 mg, and obesity (grade II). A positive family history of psoriasis was reported: his grandmother and sister had psoriasis. Over the years, our patient failed to respond to different topical and classic systemic therapies such as methotrexate and cyclosporine. In 2007, anti-TNF alpha-blockers, infliximab,

and etanercept to standard doses, were also used in standard doses. Although they gave a significant improvement, the disease relapsed during the following months of treatment. On examination, severe scaly plaques involving trunk, arms, and legs were observed (**Figure 1**). Psoriasis Assessment Score Index (PASI) was 34.2. The clinical exam did not reveal the signs of concomitant psoriatic arthritis. For the evident difficulties in management, particularly the lack of long-term efficacy, we considered to initiate a treatment with ustekinumab. Before starting the new treatment, a complete laboratory with blood count and chest x-rays were performed. No significant alterations were found. According to the patient's weight (108 kg), he was treated using 90 mg ustekinumab. A dramatic response was observed only 1 week after the first injection, reaching PASI 75 (**Figure 2**). On the following-up, the efficacy was maintained and no local subcuta-

neous reaction was observed in the injection site.

Psoriasis is a chronic, relapsing immune-mediated inflammatory disease affecting the quality of life of patients with this condition. The first-line management of this condition is with topical treatments, including vitamin D analogues, topical steroids, tar-based preparations, dithranol, and salicylic acid.<sup>2</sup> When no satisfactory result is achieved with these topical agents, systemic treatment may be initiated such as cyclosporine, methotrexate, and acitretin. Guidelines from the British Association of Dermatologists suggest that patients with psoriasis may be eligible to receive interventions with any of the 4 licensed biological agents (infliximab, etanercept, adalimumab, and ustekinumab) when they fulfil either of the following specific criteria: (i) severe clinical disease, defined as PASI  $\geq 10$ , (ii) intolerance to standard systemic therapy, (iii) contraindicated, or (iv) lack of



**Figure 1.** Severe scaly erythematous plaques involving extremities, buttocks, and lumbar area.



**Figure 2.** Dramatic improvement of lesions with ustekinumab therapy. Residual hyperpigmentation is observed.

response to standard systemic therapy.<sup>3</sup> Despite of all this full range of therapeutic approaches, the treatment of moderate-to-severe psoriasis can be challenging. As we stated previously, standard systemic therapies sometimes show initial efficacy in only a certain percentage of patients, whereas other patients are resistant to any kind of therapy. Our patient suffered from a severe form of psoriasis that was recalcitrant to other systemic therapies including anti-TNF alpha-blockers. Although the TNF-alpha has an important role in the pathogenesis of psoriasis,<sup>4</sup> recent studies over the past 5 years have altered the view of psoriasis as a disease mediated primarily by more specific cytokines, including IL-23 and IL-12. Ustekinumab is a fully human monoclonal antibody that blocks these specific molecules, thus inhibiting proliferation of Th1 and Th17 T-cells. Such a unique mechanism of action leads to the rapid onset of clinical response after the initiation of treatment, with 60% of pa-

tients attaining Physician's Global Assessment scores of "cleared" or "minimal" by week 12.<sup>5</sup> Treatment with ustekinumab was very well tolerated in our case, and it resulted in a very rapid and maintained response without any side effect. In conclusion, ustekinumab provides an effective alternative to current anti-TNF alpha preparations in psoriasis refractory to other therapies.

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## Difference in the incidence of congenital hypothyroidism among world countries

**To the Editor:** The incidence of congenital hypothyroidism (CH), which is one of the most common preventable causes of mental retardation, has been shown to vary among different parts of the world, and the global average of CH is estimated 1 per 3000 to 4000 live births.<sup>1,2</sup>

Abdelmokrader<sup>3</sup> recently conducted a population-based case-control study to investigate the risk factors of CH in Egypt and indicated that birth defects, female gender, gestational age >40 weeks, twins, and gestational diabetes were significantly associated with congenital hypothyroidism. In another population-based case-control study in Italy,<sup>4</sup> factors related to CH including birth defects, female gender, maternal diabetes, twins, preterm delivery, and gestational age >40 weeks were also confirmed. Similarly, in a

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matched case-control study in Iran, we also revealed that factors such as twin, birth season, maturity, jaundice at birth, birth weight, age at pregnancy, maternal anemia and goiter, gestational age, delivery type, father's education and smoking status, and consanguinity have an effect on the incidence rate of CH.<sup>5</sup>

All of the mentioned studies have concluded that genetic and environmental factors contribute to the etiology of CH in the region of study that may also be applicable to other developed or developing countries. Questions remain as to why some countries have a higher incidence rate of CH than others while there is a similarity in risk factors of CH among different countries. We do not know the underlying causes of this difference. These hypotheses could be tested in a global case-control study considering all the potential confounding factors. However, the results from the comparison between studies in the different parts of world led us to formulate a new hypothesis: perhaps the interaction of environmental factors and other factors on CH exists higher in some regions than in other. However, geographical differences and climate may play an important role in the occurrence of CH compare to genetic factors. A comparative evaluation in the form of a global case-control study among different countries is recommended to test the above-mentioned hypotheses.

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## RE: The burden of Rotavirus gastroenteritis among hospitalized pediatric patients in a tertiary referral hospital in Jeddah

**To the Editor:** I have 2 comments on the interesting paper by Afifi and Nabiha.<sup>1</sup>

First, despite the implementation of Rotavirus (RV) vaccine in Saudi Arabia in 2006, the prevalence of RV gastroenteritis (RVGE) (42.9%) reported by Afifi and Nabiha<sup>1</sup> is still worrisome. I presume that that the worrying prevalence can be attributed to the following 2 points: (1) Saudi pediatric population is not yet completely covered with RV vaccine. This is obvious on noticing that only 2.3% of the studied RV positive GE and 6.1% of the studied RV negative GE received RV vaccine (**Table 1**).<sup>1</sup> (2) It is obvious that temporal and spatial fluctuations in the genotype distribution of human RV are

continuously observed worldwide in surveillance studies. New genotypes, such as G9 and G12, have emerged and spread worldwide in a very short time span. In addition, reassortment events have the potential to contribute substantially to genetic diversity among human and animal RV.<sup>2</sup> Recent data on the molecular epidemiology of RVGE in Saudi children are scarce. Kheyami<sup>3</sup> addressed the distribution of G and P types of RV circulating in the population of Saudi Arabia and demonstrated the presence of serotypes G1-G4, G9, G12, P [4], P [6], and P [8]. However, Obeid<sup>4</sup> in his study found that subgroup I (serotype 2) constituted 5.4% of the isolates in comparison to 56.7% for subgroup II (serotypes 1, 3, and 4), whereas 37.8% were nontypeable. Regular surveillance and characterization of RV are, therefore, warranted to confirm RV genotype fluctuations. This, in turn, might partly explain the prevalence of RVGE in Saudi children compared to other viruses. It also helps identify unusual types that could be incorporated into future RV vaccines.

Second, Norovirus (NV) is currently recognized as one of the emerging viruses causing infection in humans. It is the leading cause of the outbreaks of viral GE worldwide. In children, NV plays an increasing and important role in enteric infection, apart from RV, especially in the post-RV vaccine era.<sup>5</sup> Afifi and Nabiha<sup>1</sup> categorized their studied GE cases into 4 groups: RV infection alone (33.6%), adenovirus (AV) infection alone (7%), combined RV and AV infection (9.3%), and other causes of GE (50.2%). I wonder whether they detected the cases of NVGE in their studied cohort and probably included them within the latter group. This is critical to comment that NVGE shares many characteristics of RVGE,

namely similar clinical presentation, significant morbidity, mortality and economic burden, and the need for regular molecular and genetic surveillance of the circulating virus.

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**Reply**

I would like to thank Prof. Al-Mendalawi for his precious comments and contribution. I guess that the author's name (Nabih) was misspelled in the comment and the citation.

As regards the first comment, we agree that the prevalence of Rotavirus gastroenteritis is still worrisome for the reasons men-

tioned in the comment. It is true that Rotavirus vaccination was implemented in Saudi Arabia since the year 2006 but the implementation in the national immunization program started in 2013. This was 3 years after our study, which was conducted in 2010. It is also true that 2.3% of our Rota positive gastroenteritis (RPG) cases were vaccinated, but 8.1% of our Rota negative gastroenteritis (RNG) cases were vaccinated as well. The correct percentage of vaccinated RNGE cases, in our study, was 8.1%, and not 6.1% as mentioned by Prof. Al-Mendalawi.<sup>1</sup> Our study recommendation stated, "In view of the high disease prevalence among children, locally and worldwide, and in view of the effectiveness of vaccination shown in the previous studies and our study, we recommend routine Rotavirus vaccination as the most effective available means of control despite improvement in sanitation and hygiene. Surveillance for the efficacy and effectiveness of vaccination as well as the differential efficacy of the 2 available vaccines is recommended." We hope that with the current vaccination program, the prevalence of RPG will dramatically decrease, and we plan to have further studies to assess the efficacy of vaccination in our community. With the recent introduction of the 2 Rotavirus vaccines, RotaTeq and Rotarix, it appears that the total number of hospitalizations due to Rotavirus infections is being reduced in many countries, at least in developed countries that implemented a universal immunization program. No data analyses are available to clarify whether the Rotavirus vaccine introduction would allow other Rotavirus P and G genotypes—which are not covered by the current vaccines—to emerge into the human population and fill the apparent gap.<sup>2</sup> Therefore

we agree with Prof. Al-Mendalawi as regards the need for regular surveillance and characterization of Rotavirus. With regard to the second comment, we agree with Prof. Al-Mendalawi about the importance of Norovirus gastroenteritis, but it was not tested in our study. We hope that it could be addressed in further studies.

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