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The role of tyrosine kinase inhibitors in tuberous sclerosis

Tuberous sclerosis (TS) is an autosomal dominant neurocutaneous syndrome characterised by widespread benign hamartomatous lesions in several organs (Shwartz *et al*, 2007; Chiarugi *et al*, 2008; Curatolo *et al*, 2008). Although the primary treatment of TS is surgical, there is growing evidence regarding medical treatment alternatives (Shwartz *et al*, 2007; Zhang *et al*, 2007; Curatolo *et al*, 2008; Huang & Manning, 2008). Given that recent studies have demonstrated a predisposition to the activation of platelet-derived growth factor receptor (PDGFR) in TS, tyrosine kinase inhibitors (TKI) seem to be an appealing treatment modality in this setting (Arbiser *et al*, 2002; Zhang *et al*, 2007).

We present a case with chronic myeloid leukaemia (CML) and TS; two different diseases, both of which have a similar pathogenetic pathway based on TK receptors. We thus anticipated that TKIs would affect the course of both CML and TS in clinical practice.

A 25-year-old female patient, with a previous diagnosis of TS, was evaluated at Gazi University Hospital for fatigue. Her physical examination was notable with pallor, splenomegaly and facial nodular lesions. A complete blood count showed haemoglobin level of 74·5 g/l, white blood cell count 391×10^9/l and platelet count 874×10^9/l. A bone marrow biopsy was hypercellular with 100% Philadelphia positive cells. She was diagnosed with chronic phase CML, and imatinib 400 mg/d was commenced. She failed to achieve any kind of response, despite the gradual increments in imatinib dose to 600 and 800 mg. As T315I mutation was negative, she was switched to dasatinib 100 mg/d and continued her antiepileptic prophylaxis. Although complete haematological and molecular response was achieved a month after starting dasatinib, there was no improvement in the frequency of her seizures, which she also used to have prior to the diagnosis of CML, and in the facial nodular lesions.

As TS is considered to be a genetic multisystem disorder expressing PDGFRs and, in particular, shares a common pathogenetic pathway with CML, we evaluated the possible role of TKIs on PDGFRs to determine whether they could alter the clinical course of TS. While CML was successfully treated with dasatinib, there were unfortunately no beneficial effects of imatinib and dasatinib on the symptoms and signs related to TS in this particular case.

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Impaired neutrophil migration and phagocytosis in IRAK-4 deficiency

Interleukin-1 receptor associated kinase-4 (IRAK-4) functions as a signal transducer downstream of multiple Toll-like receptors (TLRs). Human autosomal recessive IRAK-4 deficiency leads to impaired TLR responses in leucocytes and was recently identified as a cause of significant pyogenic bacterial infections in childhood. Curiously, the observed immunodeficiency is for a narrow range of microbes, predominantly Gram positive bacteria, especially *Streptococcus pneumoniae* (*S. pneumoniae)* and *Staphylococcus aureus (S. aureus)* and improves with age. To date, most of the leucocyte defects described are in mononuclear cells that demonstrate impaired NF-κB activation and release of inflammatory cytokines (Picard *et al*, 2003; Ku *et al*, 2007). In contrast there has been poor documentation of neutrophil function except for defective TLR-ligand-induced CD62L shedding and superoxide generation (Picard *et al*, 2003; von Bernuth *et al*, 2006;

Table I. Clinical and biological characteristics of four IRAK-4 deficient patients.

				Mutation		TLR response (PBMC)						
Patient	Clinical features	Organisms	Follow up	Nucleotide	Protein		2	3	4	5	7/8	9
PT1	Neonatal septicaemia and meningitis Fatal pneumococcal meningitis	*P. Aeruginosa* *S. Pneumoniae*	Deceased, 23 months	c.877C>T c.593 del G*	p.Gln293X p.Gly198fs*	IL-6 TNF-α	nd nd	nd nd	nd nd	nd nd	nd nd	nd nd
PT2	Neonatal scalded skin syndrome (2x)	*S. Aureus*	Alive, 2 years	c.877C>T c.593 del G*	p.Gln293X p.Gly198fs*	IL-6 TNF-α	↓↓ ↓	≈ ≈	↓↓↓ ↓↓	≈ ≈	↓↓ ↓	≈ ≈
PT3	Neonatal breast abscess Septicaemia Osteomyelitis Soft tissue cellulitis Meningitis (2x)	*S. Aureus* *H. Influenza (b)* *P. Aeruginosa* *S. Pneumoniae*	Alive, 13 years	c.877C>T	p.Gln293X	IL-6 TNF-α	↓↓↓ ↓↓	≈ ↓	↓↓↓ ↓↓↓	↓↓ ↓	↓↓↓ ↓↓	↓ ≈
PT4	Meningitis Retro-orbital inflammation Septic arthritis	*S. Pneumoniae*	Alive, 5 years	c.877C>T c.893G>A*	p.Gln293X p.Gly298Asp*	IL-6 TNF-α	↓↓↓ ↓↓	≈ ↓	↓↓ ↓	≈ ↓	↓↓ ↓	↓ ↓

↓: 5–50 fold reduction, ↓↓: 50–250 fold reduction, ↓↓↓: ≥250 fold reduction, ≈: levels similar (≤5 fold reduction) to controls.
TLR, Toll-like receptor; PBMC, peripheral blood mononuclear cells; IL-6, interleukin 6; TNF-α, tumour necrosis factor-α, nd, not determined.
*indicates novel mutations.