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Éditorial

Behçet's disease: The French recommendations

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Behçet's disease (BD) is a systemic variable vessel vasculitis [1] that involves the skin, mucosa, joints, eyes, arteries, veins, nervous system and the gastrointestinal system, presenting with remissions and exacerbations. It is a multifactorial disease, and several triggering factors including oral cavity infections and viruses may induce inflammatory attacks in genetically susceptible individuals. Investigations of inflamed tissues suggest a vasculitis or vasculopathy with mixed-cellular perivascular infiltrates and thrombotic tendency as the underlying pathology [2]. Although the etiology of BD remains unclear, recent immunogenetic findings are providing clues to its pathogenesis. In addition to the positive association of HLA-B*51, which has been confirmed in multiple populations, recent studies report additional independent associations in the major histocompatibility complex class I region. HLA-B*15, -B*27, -B*57, and -A*26 are independent risk factors for BD, while HLA-B*49 and -A*03 are independent class I alleles that are protective for BD. Genome-wide association studies have identified associations with genome-wide significance (in the IL23R-IL12RB2, IL10, STAT4, CCR1-CCR3, KLRC4, ERAP1, TNFAIP3, and FUT2 loci [3,4]. In addition, targeted next-generation sequencing has revealed the involvement of rare nonsynonymous variants of IL23R, TLR4, NOD2, and MEFV in BD [5]. These genes encompass both innate and adaptive immunity and confirm the importance of the predominant polarization towards helper T cell (Th) 1 versus Th2 cells, and the involvement of Th17 cells [6]. Neutrophils of patients with BD are hyperactivated and exhibit increased phagocytosis and superoxide production, which potentially contribute to clot formation by fibrinogen oxidation. Neutrophil extracellular traps (NETS) and markers of NETS levels are elevated in patients with BD and contribute to the procoagulant state [7]. In addition, epistasis observed between HLA-B*51 and the risk coding haplotype of the endoplasmic reticulum-associated protease, ERAP1, provides a clue that an HLA class I-peptide presentation-based mechanism contributes to this complex disease [5]. Inflammatory diseases, such as ankylosing spondylitis, psoriasis [8], psoriatic arthritis or crohn's disease [9] show strong overlap of susceptibility genes for BD and share many clinical manifestations such as oral ulcers, erythema nodosum, uveitis, arthritis, and ulcers of the colonic and ileocecal mucosa, as well as effective therapeutic agents.

Several new therapeutic modalities with different mechanisms of action have been studied in patients with BD. Substantial amount of new data were published on the management of BD, especially with biologics over the last years [10].

Apremilast is a small molecule that inhibits phosphodiesterase-4 (PDE4). PDE4 inhibition by apremilast elevates cyclic adenosine monophosphate (cAMP) levels in immune cells, which in turn downregulates the inflammatory response by reducing the expression of pro-inflammatory mediators such as TNF-α, IL-23, and INF-γ, and increased levels of anti-inflammatory cytokines, such as IL-10 [11]. Given its biological effect and the pathogenesis of BD, apremilast might be a candidate in the treatment of BD. The drug that has been essentially developed in psoriasis and psoriatic arthritis, is generally well tolerated apart from gastrointestinal side effects that are observed in around one third of patients. Depression has also been rarely reported in patients treated with apremilast.

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Apremilast has been demonstrated to be effective in treating oral ulcers, in a phase 2, placebo-controlled study in which 111 patients with BD who had two or more oral ulcers were randomized to receive 30 mg of apremilast twice daily or placebo for 12 weeks [12]. The mean number of oral ulcers per patient at week 12 (primary end point) was lower in the apremilast-group than in the placebo-group (0.5 ± 1.0 vs. 2.1 ± 2.6) ($P < .001$), with an associated major decline in pain. Despite the fact that there was a significant difference between treatment groups for pain visual analogue scale (VAS) from oral ulcer at week 12, the improvement in the number of oral ulcers was non significant for males but significant for females.

These results were also supported in a phase 3, placebo-controlled study in which 207 patients with BD who had two or more oral ulcers were randomized to receive 30 mg of apremilast twice daily or placebo for 12 weeks followed by an active treatment phase (patients switched from placebo to apremilast) through week 64 [13]. To be included, patients should have previously receieved ≥1 non-biologic therapy such as but not limited to topical corticosteroids, or systemic treatment. Topical corticosteroids, colchicine, and immunosuppressants were not allowed during the placebo-controlled period. Significantly lower oral ulcers counts ($P \leq .0015$) and oral ulcers pain ($P \leq .0035$) were observed with apremilast vs placebo from weeks 1–12 and sustained up to 64 weeks. Significantly more patients achieved complete response of oral ulcers at week 12 with apremilast vs placebo (52.9% vs 22.3%, $P < .0001$). These effects were maintained through week 64 (64.2% vs 53.3% of complete remission of oral ulcers in the apremilast and the former placebo group, respectively). Improvements decreased within 4 weeks of apremilast discontinuation. The most common adverse events with apremilast were diarrhea (41.3%), nausea (19.2%), headache (14.4%) and upper respiratory tract infection (11.5%); no new safety concerns emerged. The main limitation of this study was the lack of a comparator such as colchicine.

These important therapeutic advances in BD have led us to propose French recommendations for the management of Behcet's disease [Protocole National de Diagnostic et de Soins de la maladie de Behçet (PNDS)] [14]. These recommendations are divided into two parts: i. the diagnostic process and initial assessment and ii. the therapeutic management. Thirty key points summarize the essence of the recommendations. We highlighted the main differential diagnosis of BD according to the type of clinical involvement (oral ulcerations, bipolar ulcerations, joint, skin, gut, vascular or neurological lesions). The place of genetics is also discussed. We indicated the clinical presentations that must lead to the search for a genetic cause (early onset, family history, unexplained recurrent fever associated with an elevated CRP, digestive symptoms in the forefront, a myelodysplasia....) and specified the main genetic causes associated with a phenotype close to BD (mevalonate kinase deficiency, haploinsufficiency A20).

In addition to the now well-known autoinflammatory interleukin1 (IL-1) and interferon pathways, the range of possibilities widens with the description of negative regulation defects of the NFKB pathway. The NFKB pathway initiated upon contact of a ligand with tumor necrosis factor receptor 1 (TNFR1) plays a critical role in the initiation of the inflammatory process since it produces major cytokines such as IL-1, interleukin 6 and TNF; its downregulation is essential for stopping the inflammatory process and depends on the level of ubiquitination of TNFR1-associated proteins and other intermediate compounds. A20 is a protein that modify ubiquitination and its defect results in activation of the NFKB pathway with excessive production of proinflammatory cytokines. The haploinsufficiency of A20 (HA20) shares bipolar aphtosis and uveitis with BD, but is distinguished by its dominant transmission, an earlier disease onset, and severe gastrointestinal involvement in the foreground [15,16]. Clinical heterogeneity of HA20 is very important and patients may have concomitant or sequential autoinflammatory and autoimmune manifestations [17] during their lifetime or, more rarely, a humoral, immune deficiency. The treatment of HA20 is difficult with some efficacy of high dose steroids, anti TNF and anti IL1.

Finally, we proposed in the PNDS of BD [14] the French recommendations of therapy according to the different manifestations of BD and taking into account the therapeutic advances in the field.

Oral ulcerations which are the hallmark manifestations of BD should be first treated by symptomatic topical therapy and colchicine (1-2 mg/day). In refractory cases or intolerance to colchicine we recommend the use of apremilast (30 mg twice a day) or thalidomide.

Any posterior uveitis of BD should be treated systemically with corticosteroids and immunosuppressants. Posterior segment involvement requires the use of systemic corticosteroids and immunosuppressants, such as azathioprine for mild involvement. Severe posterior uveitis (decreased visual acuity, occlusive vasculitis and/or macular edema) warrants systemic corticosteroid and antibody therapy at TNFα. Interferon-alpha (IFN-α) may be proposed as a therapeutic alternative.

In severe parenchymatous neurological disease (Rankin score ≥ 2), an immunosuppressant should be added at the start of treatment, such as intravenous cyclophosphamide, 6 infusions every 4 weeks followed by oral azathioprine (2 to 2.5 mg/kg/day). Anti-TNFα antibodies such as infliximab may be proposed as an alternative to cyclophosphamide.

For less severe parenchymal neurological damage (Rankin score < 2), oral azathioprine is recommended. Methotrexate or mycophenolate mofetil may also be used.

It is now clearly established that immunosuppressive therapy is the cornerstone of the therapeutic strategy in severe vascular forms of BD [18]; this is based on the fact that inflammation of the vascular wall most likely plays a major role in the occurrence of vascular thrombotic lesions. Curative anticoagulation is recommended in deep venous thrombosis after assessment of the risk of hemorrhage and verification of possible arterial aneurysmal lesions. The duration of anticoagulant treatment will be 3 to 6 months except in severe forms such as thrombosis of the supra-hepatic veins and/or vena cava, which require prolonged anticoagulation.

For acute deep vein thrombosis without severity criteria (involving limbs), treatment with glucocorticoids (prednisone 0.5 mg/d as a loading dose) and effective anticoagulation for 3 to 6 months is recommended.

The treatment of severe cardiovascular diseases (thrombosis of the supra-hepatic veins, thrombosis of the vena cava, arterial aneurysms, myocarditis...) is based on high doses glucocorticoids (intravenous bolus of methylprednisolone), followed by corticosteroid therapy at 1 mg/kg/day (not to exceed 80 mg/day) of prednisone equivalent for 3 weeks with a progressive decrease (15 to 20 mg/day at 3 months and ≤ 0.1 mg/kg/day at 6 months). An immunosuppressant should be added at the start of treatment, such as intravenous cyclophosphamide (a total of 6 infusions every 4 weeks) or antibodies to TNFα (infliximab 5 mg/kg at week 0, 2, 6 and every 5 to 6 weeks or adalimumab 40 mg every two weeks).

A reduction (or discontinuation) of immunosuppressive or immunomodulatory treatment should only be discussed, except in exceptional cases, after at least 2 years of remission in the case of severe BD (ophthalmological, digestive, neurological, cardiovascular and pulmonary impairment).

With regard to other therapies, tocilizumab might be an alternative to anti-TNF agents for refractory patients.

Conflict of interest

David Saadoun has received research grant, consulting and lecturing fees from Medimmune, Bristol Meyer Squibb, Abbvie, Roche Chugai, Servier, Gilead, AstraZeneca, Glaxo Smith Kline, Sanofi Genzyme, Celgene, Janssen, Amgen and Mylan.

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