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Immune-related adverse events with bispecific T-cell engager therapy targeting B-cell maturation antigen.

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Contributions: BP, CT and BT wrote the manuscript. BP, MB, CA, TG, VD, CT, RDT, AB and BT treated the patient. RDT and BJ provided imaging data. All authors critically reviewed the manuscript.

Running title: Dysimmunity with bispecific agents targeting BCMA

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Bispecific antibodies (BispAb) targeting BCMA x CD3 has been recently approved for the treatment of patients with relapsed and refractory myeloma previously exposed to immunomodulatory drug, proteasome inhibitor, and anti-CD38 antibodies. For instance, the phase 1-2 MajesTEC-1 study demonstrated high efficacy of Teclistamab in advanced (median of 5 prior lines), triple-class exposed and refractory myeloma, with an overall response rate of 63% and median progression free survival of 11.3 months\(^1\). In BispAb studies, most common treatment-emergent adverse events were Cytokine Release Syndrome (CRS), hematological toxicities and Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS). Dysimmune events were not observed nor classified as such but were exclusion criteria for protocol enrollment\(^2\). Immune-related adverse events (irAEs) are well described for the immune checkpoint inhibitor therapy such as anti-PD1 or anti-CTLA-4. This type of adverse events could affect different organs, such as gastrointestinal, endocrinological, skin or rheumatological systems\(^3\). The explanation of these irAEs under checkpoints inhibitors seems straightforward with T-cells’ activity enhancement\(^3\). Thus, through two thoroughly documented clinical cases, we report here how dysimmunity could be induced by T-cell engaging BispAb, with very different patterns of symptoms.

This is a 77-year-old woman without significant medical history, who has been treated for IgG Kappa multiple myeloma. Her 9\(^{th}\) line consisted of a CD3xBCMA BispAb, a stringent complete remission (sCR) from the 13\(^{th}\) cycle was obtained. A grade 1 CRS was noted at 1st cycle, resolutive. Shortly after sCR, the patient presented with recurring oligoarthritis. There was a biological inflammatory syndrome (CRP increased and thrombocytosis). Blood cultures were positive twice for *Neisseria cinerea*, and while echocardiography showed no signs of infective endocarditis, she has been treated with Ceftriaxone (2g/d) for 14 days and the oligoarthritis resolved (figure 1). The PET-CT that had been performed for the disease’s
extension showed Grade III (highest grade) parietal hypermetabolism of the thoracic aorta, brachiocephalic artery trunk, right subclavian artery, and left common iliac artery (figure 2I). On examination, no recent or previous cephalic, visual, mandibular, or rhizome manifestations, no chest, back, abdominal, or lumbar pain with an inflammatory appearance were observed. The temporal and peripheral pulses were perceived without vascular murmur. Except moderate inflammatory syndrome with a CRP of 8 mg/l, blood results were normal. Blood cultures and infectious serologies were negative. Systematic etiological exams for inflammatory vasculitis were negative. The temporal artery biopsy didn’t demonstrate Horton's disease. Ultrasound-doppler of the encephalic and temporal arteries demonstrated a significant diffuse hyperplasia of the intima, at the origin of the right subclavian artery. A segmental inflammatory aspect of the trunk of the left temporal artery with halo sign was also noticed. Given the context of severe immunosuppression and recent infection, this arteritis was presumed to be related to an infectious cause, relying on Ceftriaxone treatment to recover. No improvement of PET-CT findings at 8 weeks from arteritis diagnosis were noted. It was decided to start a 2nd line therapy with Cotrimoxazole for 8 weeks. The patient underwent a new PET-CT after 2 months, with no improvement (PETVasc global 27/48). PETVasc is an additional score with a maximum score at 48 (figure 2I). A systemic corticosteroid therapy at a dose of 0.7 mg/kg/day in progressive decrease over 12 months was introduced (figure 1). Several PET-CT showed a clear decrease in segmental hyperfixation of the wall of large and medium-sized vessels (PETVasc global 23/48) (figure 2I). End-of-treatment PET-CT, performed just after steroid withdrawal, showed an iconographic relapse. Referring to the Teclistamab-induced vasculitis, internists introduced Tocilizumab subcutaneous weekly, with maintaining corticotherapy. Teclistamab was stopped during the first month (figure 1).
The other case reported here concerns a 66-year-old woman with a notable history of immune thrombocytopenia (ITP) refractory to corticosteroid (splenectomy in 1995). She has been diagnosed with a symptomatic multiple myeloma, treated with 5 lines. After the 1st cycle of CD3xBCMA BispAb, a grade 1 CRS with ITP decompensation (resolved with IV Ig) was observed. At the beginning of cycle 11, the patient presented with an abrupt polyarticular presentation with distal interphalangeal joint (DIJ) and proximal interphalangeal joint (PIJ) swelling of the 3rd and 2nd fingers of the left hand, as well as the carpometacarpal joint (CMJ) of the 2nd finger of the left hand. Pain of the left knee and hip, with morning rusting were also notified. At the beginning of the 12th cycle, the inflammatory rhythmed polyarthralgias were still present, but migratory with swelling of the ankles too. No family history of inflammatory rheumatism, no uveitis, no dactylitis, no transit abnormalities were reported. Blood testing was normal for uric acid. The immune checkup came back as negative (antinuclear antibodies, rheumatoid factors and anti-CCP) as well as infectious investigations (blood culture, hepatitis PCRs). On X-rays, there were some erosions suspected as consequences of inflammation without argument for chondrocalcinosis or osteoarthritis. On US (figure 2II), there was a grade II synovitis of wrists and PIJ. Furthermore, there was a tenosynovitis of the common extensors of the fingers and there were bilateral crural synovitis and fibular tenosynovitis of the ankles. The patient has been recovering gradually under corticosteroid therapy introduced as 10 mg per day with a continuous tapering. From the 1st dose decrement, complete regression of the morning rusting in the lower limbs was observed, followed by disappearance of hands and wrist synovitis symptoms. Teclistamab was discontinued 3 months. (figure 1).

These two cases illustrate two presumed irAEs due to BispAb during multiple myeloma treatment. Indeed, in the first case, it seems particularly challenging to decipher whether it is a
primary inflammatory vasculitis or potentially induced by BispAb. However, the germ involved here, which usually damages the little vessel walls directly, has been controlled by prolonged antibiotic therapy and is therefore unlikely to be the cause of persistent vasculitis. Relating those events with drug exposure may be contra-intuitive as most AEs related to BispAb are on the side of immunosuppression. Indeed, it may seem paradoxical that an antibody targeting BCMA can induce autoimmune reactions while some drugs targeting its soluble receptor/ligand (BAFF) is used to treat autoimmune disease with Belimumab for instance, this situation has been extensively described for anti-TNF alpha therapy in *genesis lupus*. Biological rationale may enlighten this particular course of events. To remember, BCMA is a transmembrane receptor naturally expressed on plasma cells and is consistently expressed at high levels on malignant plasma cells. BCMA binds to BAFF, a cytokine expressed by B-lineage cells, and leads to the activation of kinases (MAPK8/JNK) by NFκB transcription that stimulate plasma cells to maintain humoral immunity. BAFF is required for normal B-cell homeostasis, but it also promotes the survival of malignant B-cells. BCMA can also bind to a related protein, APRIL involved in B cell development and autoimmune response. The complex interactions between BCMA and its ligands BAFF and APRIL explain BCMA implication in the maintenance of plasma cells, but also in several cancers, autoimmune and infectious diseases. This effect could be explained by the increase of the BCMA’s ligands levels along with the inhibition of its receptor via bispecific therapies in multiple myeloma (CD3-BCMA). BCMA may give rise to dysimmune disease via its targeting. Supporting this hypothesis, BCMA deficiency in mice exacerbated phenotypes with dysimmune diseases (table 1). Different studies have shown that serum levels of BAFF were associated with a major disease activity. When BCMA is allosterically occupied, other BCMA ligands could increase, and would likely bind to its targets (BAFF-R and APRIL-R) (table 1). Indeed, this explains why some immunotherapy treatments for autoimmune diseases
(such as lupus or vasculitis\textsuperscript{10}), take leverage of this effect, such as Atacicept\textsuperscript{11} which targets both BAFF and APRIL-R; or Tabalumab\textsuperscript{12} which also targets both BAFF and BCMA.

The second hypothesis for the development of post-BCMA autoimmunity could be explained by the expansion of follicular T helper cells. Indeed, the uncontrolled expansion of T follicular helper cells (TFH) activates autoreactive B cells to produce antibodies inducing autoimmunity. TFH cells express BCMA and BR3 receptors and accumulate in the spleen when BCMA is absent. BCMA deficiency in T cells can promote TFH cell expansion, autoantibody production, and IFN\textsubscript{\gamma} production by TFH cells via BR3\textsuperscript{13}. In an experimental study\textsuperscript{13}, blocking BAFF or IFN\textsubscript{\gamma} \textit{in vivo} reduced TFH cell accumulation and improved autoimmunity in BCMA-deficient animals but not in BR3-deficient ones. BCMA acts intrinsically to T cells to limit the number of autoreactive TFH, and thereby regulates autoreactive B cell responses\textsuperscript{14}. BAFF blocking agents could be evaluated to reduce autoimmune reactions related to BCMAxC3 BispAb. However, we cannot neglect that there were no strong reports of dysimmunity with other anti-BCMA therapies as cytotoxic coupled-agents (\textit{eg}, Belantamab Mafodotin) or CAR-T cells (\textit{eg}. Ide-cel or Cilta-cel). Thus, we can hypothesize that bispecific agents with T-Cell engagement may increase unspecific T-cell response or reverse T-cells exhaustion\textsuperscript{15}, leading to dysimmunity. Against this assumption, dysimmune events with using other BispAb (targeting GPRC5D or FcRH5) were not reported. Thus, incidence and physiopathology of these dysimmune complications need to be explored in prospective studies with more patients and longest follow-up.
References


<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Mouse strain</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAFF</td>
<td>NZM2328</td>
<td>Delay in autoantibodies</td>
</tr>
<tr>
<td>BCMA</td>
<td>Nba2.Yaa</td>
<td>Enhances autoantibodies and exacerbates disease</td>
</tr>
</tbody>
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|           | NZM2328      | Increased spleen size  
No effect on autoantibodies, plasma cells or mortality |

**Table 1**: Effects of BAFF’s or BCMA’s lack in murine lupus model, table adapted with permission from Immunological Reviews *(extract from Jackson SW, Davidson A. BAFF inhibition in SLE-Is tolerance restored? Immunol Rev. 2019 Nov;292(1):102-119)*
Figure 1: Clinical, radiological, and therapeutical chronology of the two case reports

Figure 2: Cases PET and ultrasound pictures
1st case

M0 → M12
- Cotrimoxazole
- Systemic corticosteroid therapy
- Ceftriaxone
- Tocilizumab
- Stop Teclistamab

M12 → M24
- Blood cultures

2nd case

M0 → M12
- Systemic corticosteroid therapy

M12 → M24
- Stop Teclistamab

M24 → M36
- First rhumatologic events