Clinical Immunology 206 (2019) 1–2

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Editorial

Targeting cytokines to treat autoimmunity

A B S T R A C T

Monoclonal antibodies, small molecules and soluble receptors that target cytokines have revolutionized the treatment of autoimmune and autoinflammatory diseases. The articles that are presented in this special issue of Clinical Immunology analyze the basic science, the clinical implications and the future directions of cytokine targeting in these diseases.

Going back to the 1940s, it was recognized that leucocytes produce circulating factors that cause several of the hallmarks of inflammation such as fever [1]; these were later called interleukins. Since then interleukins, interferons, tumor necrosis factors and other immune signaling molecules have been functionally and structurally characterized, and are collectively called cytokines. Critical in defense against infectious agents, cytokines were later recognized as targetable orchestrators of autoimmune and autoinflammatory responses.

As biotechnology grew by leaps and bounds in the 1980s, monoclonal antibodies and soluble receptors were developed and used to neutralize Tumor Necrosis Factor alpha (TNF-α) and Interleukin (IL)-1 in the 1990s. Since then, the list of cytokines that can be blocked or in some cases infused has grown exponentially alongside disease states that can benefit from such interventions. Arguably these treatment approaches that are targeted and not globally immune-suppressive, have changed the natural history of such chronic inflammatory diseases as Rheumatoid Arthritis (RA), Inflammatory Bowel Disease (IBD) and Familial Mediterranean Fever (FMF).

wRA was the first autoimmune disease to benefit from such methods. Animal models suggested that IL-1 may be the most promising therapeutic target in RA but it was the anti-TNFα inhibitors that really changed the treatment paradigm [2]. Similarly, IBD patients with severe disease such as fistulizing Crohn's, were successfully treated with infusions of anti-TNFα antibodies. It became apparent though that a third to as high as half the patients do not respond to these modalities or lose the response over time. Fortunately, inhibition of IL-6 in the case of RA and IL-23 in IBD [3] have proven to be viable alternatives to TNF-α inhibition.

TNF-α targeting is also a very efficacious treatment in psoriasis and psoriatic arthritis (PsA). But, as it the case with RA and IBD, a significant proportion of patients is or becomes resistant to this approach. Nguyen et al [5] show that the IL-23/IL-17 pathway is upregulated in PsA and its targeting represents an alternative if not a better approach to TNF-α inhibition.

As discussed above, IL-1 was one of the first cytokines to be targeted but found to be a suboptimal therapeutic approach in RA. It was quickly recognized though that IL-1 is the main driver of the destructive inflammatory response in a cluster of diseases, collectively called autoinflammatory. In this issue, Hausmann [6] describes the transformative use of anti-IL1 therapies in autoinflammatory diseases and goes over alternatives and novel targets such as TNF-α and IL-18.

IL-6 inhibition in combination with corticosteroids has proven to be an important alternative to corticosteroid monotherapy for the treatment of large vessel vasculitis. Weyand et al [4] though point out that while suppressing the systemic symptoms and signs of the disease, IL-6 inhibition may not be as efficacious in arterial wall inflammation where other mechanisms are at play.

More challenging has been the development of targeted therapies in Systemic Lupus Erythematosus (SLE). Belimumab, a biologic targeting the B Lymphocyte stimulator is the only targeted therapy that has been approved to date. As the need for novel therapies is high, Adamichou et al [7] critically evaluate the potential of blocking cytokines in the treatment of SLE. Similar to SLE, the treatment of Antiphospholipid Syndrome (APLS) has not advanced beyond anticoagulation [9]. Dorbowolski and Erkan go over our current understanding of the condition and the potential for the development of disease modifying agents.

Finally, Mizui [8] describes the function of IL-2, a cytokine that can be both immune activating and immune suppressive. High dose IL-2 infusions were initially used to boost the immune response against cancers but, when infused at low doses, IL-2 becomes immune suppressive by inducing Treg. This immunoregulatory activity led to its use in Graft Versus Host Disease (GVHD) and more recently in SLE.

In this special issue we highlight how scientific discovery and technological advancement led to life-saving medications for millions of patients with autoimmune and autoinflammatory diseases. Progress has been uneven though with conditions such as SLE or APLS having few or no targeted disease modifying drugs. Therefore, the articles that we compiled herein not only touch on the current therapeutic landscape, but also address challenges and point to promising future therapies.

Financial support information

None.

References

[1] E. Atkins, W.B. Wood Jr., Studies on the pathogenesis of fever. II. Identification of an endogenous pyrogen in the blood stream following the injection of typhoid vaccine,

https://doi.org/10.1016/j.clim.2019.108251

Available online 21 August 2019

J. Exp. Med. 102 (1955) 499–516.
[2] V.L. Bui, E. Brahn, Cytokine targeting in rheumatoid arthritis, Clin. Immunol. (Apr 3 2018), https://doi.org/10.1016/j.clim.2018.04.001 (pii: S1521-6616(18)30180-3, Epub ahead of print).
[3] K.H. Katsanos, K. Papamichael, J.D. Feuerstein, D.K. Christodoulou, A.S. Cheifetz, Biological therapies in inflammatory bowel disease: Beyond anti-TNF therapies, Clin. Immunol. (Mar 12 2018), https://doi.org/10.1016/j.clim.2018.03.004 (pii: S1521-6616(17)30901-4, Epub ahead of print).
[4] C.M. Weyand, R. Watanabe, H. Zhang, M. Akiyama, G.J. Berry, J.J. Goronzy, Cytokines, growth factors and proteases in medium and large vessel vasculitis, Clin. Immunol. (Feb 14 2019), https://doi.org/10.1016/j.clim.2019.02.007 (pii: S1521-6616(19)30023-3, Epub ahead of print).
[5] C.T. Nguyen, Y. Bloch, K. Skladanowska, S.N. Savvides, I.E. Adamopoulos, Pathophysiology and inhibition of IL-23 signaling in psoriatic arthritis: A molecular insight, Clin. Immunol. (Sep 6 2018), https://doi.org/10.1016/j.clim.2018.09.002 (pii: S1521-6616(18)30476-5, Epub ahead of print).
[6] J.S. Hausmann, Targeting cytokines to treat autoinflammatory diseases, Clin. Immunol. (Oct 28 2018), https://doi.org/10.1016/j.clim.2018.10.016 (pii: S1521-6616(18)30432-7, Epub ahead of print).
[7] C. Adamichou, S. Georgakis, G. Bertsias, Cytokine targets in lupus nephritis: Current and future prospects, Clin. Immunol. (Sep 2 2018), https://doi.org/10.1016/j.clim.2018.08.013 pii: S1521-6616(18)30280-8, Epub ahead of print.
[8] M. Mizui, Natural and modified IL-2 for the treatment of cancer and autoimmune diseases, Clin. Immunol. (Nov 8 2018), https://doi.org/10.1016/j.clim.2018.11.002 (pii: S1521-6616(18)30624-7, Epub ahead of print).
[9] C. Dobrowolski, D. Erkan, Treatment of antiphospholipid syndrome beyond anticoagulation, Clin. Immunol. (Mar 3 2018), https://doi.org/10.1016/j.clim.2018.03.001 (pii: S1521-6616(18)30119-0, Epub ahead of print).

Vasileios C. Kyttaris*
Division of Rheumatology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
E-mail address: vkyttari@bidmc.harvard.edu.

* Corresponding author at: 330 Brookline Ave, CLS-936, Boston, MA 02215, USA.