CHAPTER 10

CANAKINUMAB USES IN DERMATOLOGY

Bilge Bülbül Şen, MD

INTRODUCTION

Canakinumab is a recombinant human monoclonal antibody of the IgG1/κ against interleukin 1β (IL-1β).[1] Novartis Pharma provides the drug as "Ilaris." Canakinumab substantially suppresses inflammation by neutralizing IL-1β signaling, so the drug has been evaluated in several autoimmune and autoinflammatory diseases that are implicated with dysregulated IL-1β activity.[2] In June 2009, the United States Food and Drug Administration approved canakinumab for the treatment of cryopyrin-associated periodic syndromes (CAPS) in adults and children over 4 years of age. In May 2013, the drug was approved for the treatment of active systemic juvenile idiopathic arthritis in patients aged 2 years and older.

To date, there are many published case reports or clinical trials assessing the effects of canakinumab in CAPS,[3] systemic juvenile idiopathic arthritis,[4] rheumatoid arthritis,[5] gout arthritis,[6] familial Mediterranean fever,[7] Schnitzler syndrome,[8] Blau Syndrome,[9] cardiovascular diseases,[10] and diabetes.[11] Moreover, canakinumab has also been reported to have potential effects in the treatment of some disorders related to dermatology, such as Behçet's disease,[12] urticarial vasculitis,[13] pyoderma gangrenosum and hidradenitis suppurativa (Table 1).[14]

TABLE 1. Clinical uses of canakinumab

FDA Approved Indications	Off-Label Uses
Cryopyrin-associated periodic syndromes	Dermatological uses
Familial Cold Auto-Inflammatory Syndrome	Schnitzler syndrome
Muckle-Wells Syndrome	Behçet's Disease
Systemic Juvenile Idiopathic Arthritis	Urticarial Vasculitis
	Pyoderma Gangrenosum
	Hidradenitis Supprativa
	Other
	Rheumatoid Arthritis
	Gout Arthritis
	Familial Mediterranean Fever
	Blau Syndrome
	Cardiovascular Diseases
	Diabetes

Mechanism of action

Interleukin-1 (IL-1) includes a group of cytokines that activate the expression of several pro-inflammatory genes.[2] IL-1β is a pro-inflammatory cytokine that located in the IL-1 family of genes. IL-1β plays a role as a mediator in the peripheral immune response during infection and inflammation. Furthermore, it has an influence on acute and chronic autoimmune diseases, diabetes, pain, and neurological disorders.[15]

IL-1β is initially produced in the form of a precursor peptide as pro-IL-1β, which is then processed in the protein complex inflammasome NLRP3/cryopyrin by caspase-1, and active IL-1β is released outside the cell.[2] Several cell types, such as macrophages, keratinocytes, fibroblasts, microglia, astrocytes, mast cells, endothelial cells, neuronal cells and Schwann cells, can secrete IL-1β.[16] IL-1β should bind the interleukin 1 receptor (IL-1-R1) and an accessory protein to exhibit pro-inflammatory effects. These receptors constitute a complex required for signal transduction at the cell membrane.[17] Canakinumab selectively binds to ILβ-1 before it interacts with its receptor complex, and inactivates its signaling. Canakinumab has advantages over the other IL-1 blockers. Since canakinumab has no cross-reactivity with IL-1α nor with the IL-1-R1 receptor, it does not affect the other IL-1-activated pathways, as do anakinra and rilonacept.[8] It has a longer half-life (26 days), so canakinumab can be used at less frequent intervals. Additionally, it has a low incidence of injection-site reactions.[2, 18]

Clinical uses

Cryopyrin-associated periodic syndromes

The cryopyrin-associated periodic syndromes (CAPS) or cryopyrinopathies include three clinically overlapping, IL-1-associated, autoinflammatory disorders:

- Familial cold auto-inflammatory syndrome (FCAS)
- Muckle-Wells syndrome (MWS)
- Neonatal-onset multisystem inflammatory disorder or chronic infantile neurologic cutaneous and articular syndrome (CINCA)

patients with infections or the risk of developing infections due to their comorbidities. The use of canakinumab is not recommended during an active severe infection, and if a serious infection develops during treatment, the drug should be discontinued. Additionally, canakinumab should not be administered in the presence of hypersensitivity to the active substance or to any of the excipients.[35]

Immunogenicity

Canakinumab has a low immunogenicity potential. In general, no immunogenicity against the drug was detected in studies. Antibodies against canakinumab were reported at a low rate in some publications, but it was reported that no neutralizing antibodies were detected and a relationship with antibody development and clinical response or adverse events was not observed.[1, 3, 4]

Drug Interactions

No formal drug interaction studies have been conducted with canakinumab. The common concomitant medications, such as paracetamol, non-steroidal anti-inflammatory drugs, systemic corticosteroids, methotrexate, antibacterials and iron supplements, do not influence the pharmacokinetics of canakinumab because the elimination mechanisms of monoclonal antibodies are different. However, the cytochrome P450 system is suppressed during chronic inflammation and canakinumab can be expected to indirectly affect the enzyme levels. Therefore, there is a possibility of increased clearance of coadministered drugs that are cytochrome P450 system substrates.[1] Additionally, the concomitant use of canakinumab and TNF inhibitors or other drugs that block IL-1 is not recommended due to increased risk of serious infections. Furthermore, live vaccines should not be administered simultaneously with canakinumab.[35]

Use in Pregnancy and Lactation

Although there are no studies regarding use during pregnancy, it is stated that canakinumab can be used during pregnancy under required conditions, and the pregnancy category is C. Caution should be exercised when administered to women who are breast-feeding.[35]

Future Prospects

Every day, experience with canakinumab is growing and new uses are being discovered. There are ongoing and completed studies on the use of canakinumab for different disorders, such as chronic idiopathic urticaria, chronic obstructive pulmonary disease, atherosclerosis, atrial fibrillation, diabetic retinopathy, age-related macular degeneration, dry eye, osteoarthritis, and polymyalgia rheumatica.[37, 38] In the future it will be better understood whether the drug will be an alternative treatment choice for other inflammatory diseases. Further studies are needed to better characterize the efficacy of canakinumab in the treatment of dermatological disorders.

REFERENCES

1. Chakraborty A, Tannenbaum S, Rordorf C, Lowe PJ, Floch D, Gram H, et al. Pharmacokinetic and pharmacodynamic properties of canakinumab, a human anti-interleukin-1beta monoclonal antibody. Clin Pharmacokinet. 2012;51(6):e1-18.
2. Dhimolea E. Canakinumab. MAbs. 2010;2(1):3-13.
3. Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, Leslie KS, Hachulla E, Quartier P, et al. Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med. 2009;360(23):2416-25.
4. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012;367(25):2396-406.
5. Alten R, Gomez-Reino J, Durez P, Beaulieu A, Sebba A, Krammer G, et al. Efficacy and safety of the human anti-IL-1beta monoclonal antibody canakinumab in rheumatoid arthritis: results of a 12-week, Phase II, dose-finding study. BMC Musculoskelet Disord. 2011;12:153.
6. Schlesinger N, Alten RE, Bardin T, Schumacher HR, Bloch M, Gimona A, et al. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. Ann Rheum Dis. 2012;71(11):1839-48.
7. Ozcakar ZB, Ozdel S, Yilmaz S, Kurt-Sukur ED, Ekim M, Yalcinkaya F. Anti-IL-1 treatment in familial Mediterranean fever and related amyloidosis. Clin Rheumatol. 2014.
8. Vanderschueren S, Knockaert D. Canakinumab in Schnitzler syndrome. Semin Arthritis Rheum. 2013;42(4):413-6.
9. Simonini G, Xu Z, Caputo R, De Libero C, Pagnini I, Pascual V, et al. Clinical and transcriptional response to the long-acting interleukin-1 blocker canakinumab in Blau syndrome-related uveitis. Arthritis Rheum. 2013;65(2):513-8.
10. Ridker PM, Thuren T, Zalewski A, Libby P. Interleukin-1beta inhibition and the prevention of recurrent cardiovascular events: rationale and design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). Am Heart J. 2011;162(4):597-605.
11. Howard C, Noe A, Skerjanec A, Holzhauer B, Wernsing M, Ligueros-Saylan M, et al. Safety and tolerability of canakinumab, an IL-1beta inhibitor, in type 2 diabetes mellitus patients: a pooled analysis of three randomised double-blind studies. Cardiovasc Diabetol. 2014;13:94.
12. Vitale A, Rigante D, Caso F, Brizi MG, Galeazzi M, Costa L, et al. Inhibition of interleukin-1 by canakinumab as a successful mono-drug strategy for the treatment of refractory Behcet's disease: a case series. Dermatology. 2014;228(3):211-4.
13. Krause K, Mahamed A, Weller K, Metz M, Zuberbier T, Maurer M. Efficacy and safety of canakinumab in urticarial vasculitis: an open-label study. J Allergy Clin Immunol. 2013;132(3):751-4 e5.

14. Jaeger T, Andres C, Grosber M, Zirbs M, Hein R, Ring J, et al. Pyoderma gangrenosum and concomitant hidradenitis suppurativa--rapid response to canakinumab (anti-IL-1beta). Eur J Dermatol. 2013;23(3):408-10.

15. Dinarello CA. Therapeutic strategies to reduce IL-1 activity in treating local and systemic inflammation. Curr Opin Pharmacol. 2004;4(4):378-85.

16. Ren K, Torres R. Role of interleukin-1beta during pain and inflammation. Brain Res Rev. 2009;60(1):57-64.

17. Dubois EA, Rissmann R, Cohen AF. Rilonacept and canakinumab. Br J Clin Pharmacol. 2011;71(5):639-41.

18. Miyamae T. Cryopyrin-associated periodic syndromes: diagnosis and management. Paediatr Drugs. 2012;14(2):109-17.

19. Yu JR, Leslie KS. Cryopyrin-associated periodic syndrome: an update on diagnosis and treatment response. Curr Allergy Asthma Rep. 2011;11(1):12-20.

20. Lachmann HJ, Lowe P, Felix SD, Rordorf C, Leslie K, Madhoo S, et al. In vivo regulation of interleukin 1beta in patients with cryopyrin-associated periodic syndromes. J Exp Med. 2009;206(5):1029-36.

21. Kone-Paut I, Lachmann HJ, Kuemmerle-Deschner JB, Hachulla E, Leslie KS, Mouy R, et al. Sustained remission of symptoms and improved health-related quality of life in patients with cryopyrin-associated periodic syndrome treated with canakinumab: results of a double-blind placebo-controlled randomized withdrawal study. Arthritis Res Ther. 2011;13(6):R202.

22. Kuemmerle-Deschner JB, Hachulla E, Cartwright R, Hawkins PN, Tran TA, Bader-Meunier B, et al. Two-year results from an open-label, multicentre, phase III study evaluating the safety and efficacy of canakinumab in patients with cryopyrin-associated periodic syndrome across different severity phenotypes. Ann Rheum Dis. 2011;70(12):2095-102.

23. Russo RA, Melo-Gomes S, Lachmann HJ, Wynne K, Rajput K, Eleftheriou D, et al. Efficacy and safety of canakinumab therapy in paediatric patients with cryopyrin-associated periodic syndrome: a single-centre, real-world experience. Rheumatology (Oxford). 2014;53(4):665-70.

24. Pesek R, Fox R. Successful treatment of Schnitzler syndrome with canakinumab. Cutis. 2014;94(3):E11-2.

25. de Koning HD, Schalkwijk J, van der Ven-Jongekrijg J, Stoffels M, van der Meer JW, Simon A. Sustained efficacy of the monoclonal anti-interleukin-1 beta antibody canakinumab in a 9-month trial in Schnitzler's syndrome. Ann Rheum Dis. 2013;72(10):1634-8.

26. Caso F, Costa L, Rigante D, Lucherini OM, Caso P, Bascherini V, et al. Biological treatments in Behcet's disease: beyond anti-TNF therapy. Mediators Inflamm. 2014;2014:107421.

27. Hamzaoui K, Hamza M, Ayed K. Production of TNF-alpha and IL-1 in active Behcet's disease. J Rheumatol. 1990;17(10):1428-9.

28. Pay S, Erdem H, Pekel A, Simsek I, Musabak U, Sengul A, et al. Synovial proinflammatory cytokines and their correlation with matrix metalloproteinase-3 expression in Behcet's disease. Does interleukin-1beta play a major role in Behcet's synovitis? Rheumatol Int. 2006;26(7):608-13.

29. Ugurlu S, Ucar D, Seyahi E, Hatemi G, Yurdakul S. Canakinumab in a patient with juvenile Behcet's syndrome with refractory eye disease. Ann Rheum Dis. 2012;71(9):1589-91.

30. Cantarini L, Vitale A, Borri M, Galeazzi M, Franceschini R. Successful use of canakinumab in a patient with resistant Behcet's disease. Clin Exp Rheumatol. 2012;30(3 Suppl 72):S115.

31. Lipsker D, Lenormand C. [Indications and modes of use for interleukin (IL)-1 antagonists in inflammatory dermatosis: a new therapeutic approach to immune-mediated inflammatory diseases]. Ann Dermatol Venereol. 2012;139(6-7):459-67.

32. Brenner M, Ruzicka T, Plewig G, Thomas P, Herzer P. Targeted treatment of pyoderma gangrenosum in PAPA (pyogenic arthritis, pyoderma gangrenosum and acne) syndrome with the recombinant human interleukin-1 receptor antagonist anakinra. Br J Dermatol. 2009;161(5):1199-201.

33. Braun-Falco M, Kovnerystyy O, Lohse P, Ruzicka T. Pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH)--a new autoinflammatory syndrome distinct from PAPA syndrome. J Am Acad Dermatol. 2012;66(3):409-15.

34. Geusau A, Mothes-Luksch N, Nahavandi H, Pickl WF, Wise CA, Pourpak Z, et al. Identification of a homozygous PSTPIP1 mutation in a patient with a PAPA-like syndrome responding to canakinumab treatment. JAMA Dermatol. 2013;149(2):209-15.

35. Ilaris Prescribing Information. [April 2, 2015]. Available from: https://www.pharma.us.novartis.com/product/pi/pdf/ilaris.pdf.

36. Cantarini L, Lopalco G, Caso F, Costa L, Iannone F, Lapadula G, et al. Effectiveness and tuberculosis-related safety profile of interleukin-1 blocking agents in the management of Behcet's disease. Autoimmun Rev. 2015;14(1):1-9.

37. Canakinumab, US National Institutes of Health, ClinicalTrials.gov [April 2, 2015]. Available from: https://clinicaltrials.gov/ct2/results?term=canakinumab&Search=-Search.

38. ACZ885, US National Institutes of Health, ClinicalTrials.gov [April 2, 2015]. Available from: https://clinicaltrials.gov/ct2/results?term=ACZ885&Search=Search.