Role of Interleukin-17 in Immunopathology of Chronic and Aggressive Periodontitis

Anand Narayanrao Wankhede, Prasad Vijayrao Dhadse

Interleukin-17 (IL-17) is a pro-inflammatory cytokine which is derived from T-cells. It is a strong agent of inflammation in inflammatory condition including the periodontitis. Several studies have focused on finding the role of IL-17 in the initiation and progression of chronic periodontitis and aggressive periodontitis (AgP). The aim of this review is to analyze the role of IL-17 in immunopathology of chronic periodontitis and AgP. An electronic literature search was conducted in the PubMed database using keywords aggressive, chronic, cytokine, IL-17, and periodontitis. A total of 152 publications were identified, wherein 43 studies fulfilled the inclusion criteria which were included and data extraction was done. Findings of these studies indicate that IL-17 is the important cytokine which plays a crucial role in the initiation and progression of periodontitis. More studies in all ethnic groups are necessary and hence that the predictive value (cutoff) of IL-17 levels in chronic and AgP can be determined.

Keywords: Aggressive, chronic, cytokine, interleukin-17, periodontitis

It has been found that IL-17 plays a vital role in the progression of the periodontitis, but the role of the IL-17 is same in aggressive as well as chronic periodontitis. Therefore, the aim of this review is to analyze the role of IL-17 in the immunopathology of these two conditions.

Methodology

An electronic literature search was conducted in PubMed database using keywords aggressive, chronic, cytokine, interleukin-17 (IL-17), and periodontitis were done. A total of 152 publications were identified, wherein 43 studies fulfilled the inclusion criteria which were included, and data extraction was done. (a) Studies which were performed in AgP patients, chronic periodontitis patients using gingival crevicular fluid
and periodontal tissues, (b) studies performed on the periodontal microorganism, inflammatory systemic condition in relation with IL-17, and (c) Effect of periodontal therapy on IL-17 were included to write review. Exclusion criteria included studies performed on smokers, diabetes mellitus, and saliva [Flow chart I].

**MECHANISM OF ACTION OF CYTOKINES**

Cytokines communicate in network, first by activating each other followed by transmodulating cell surface receptors and finally by synergistic, additive, or antagonistic interactions on cell action. The intensity, extent, and resolution of any inflammation depend on the shift in balance between the action of pro-inflammatory and anti-inflammatory cytokines. The term “interleukins” have been replaced the term “cytokines” due to their role in communication between leukocytes.

Some cytokines exhibit autocrine function (binding to the cell that produced them) or paracrine (binding to nearby cells) or endocrine (binding to distant cells). Cytokines may be pleiotropic, i.e., eliciting different biological activities on different cells. Different cytokines are grouped into families with respect to genome location, gene, and protein structure. It is important to note that members of the same family do not necessarily exhibit similar biological effects.

Cytokines are further classified into pro-inflammatory and anti-inflammatory cytokines and balance between them is crucial for determining disease initiation and progression. Cytokines are considered as a key component to the pathogenesis of any inflammatory diseases and play an important role in the initiation, progression, and alternation in host modulation of any inflammatory disease including periodontal inflammation. Lipopolysaccharide and other toxin products released by bacteria lead to the stimulation of host cells resulting in the release of cytokines. Cytokine network takes control over inflammatory mechanism to trigger or suppress tissue reactions.

**T-CELLS AND INTERLEUKIN-17**

T helper (Th) cells are divided into Th1 and Th2 subtypes according to their cytokine profiles and have different functional properties. Th1 cells activate cellular immunity and the production of pro-inflammatory cytokines. Th2 cells induce B-cell-mediated humoral immunity and anti-inflammatory cytokine patterns. Recently, IL-17-producing cell named as Th17 was identified which is a subset of CD4+ T-cells. Th-17 cell plays an important role in protective antibacterial host response.

IL-17 is a pro-inflammatory cytokine and was first described as T-cell product in 1993. The family consists of the following six members: IL-17A, B, C, D, E (IL-25), and IL-17F which are structurally associated. The genes for IL-17A and IL-17F are located on chromosome 6q. IL-17B gene is located on chromosome 5q. Genes for IL-17C, IL-17D, and IL-17E are located on chromosome 16q, 13q, and 14q arm, respectively. IL-17 is 17-kd protein that is secreted as a dimer. IL-17 shares no sequence homology with other known mammalian proteins, and therefore, constitute as a specific cytokine family. IL-17 acts through cell-membrane receptors. Various effects of interleukin-17 on cell populations in human body are mention in Table 1.

**ROLE OF INTERLEUKIN-17 ON OTHER CYTOKINES**

IL-17 is also responsible to stimulate other pro-inflammatory cytokines such as IL-1 β, IL-6, IL-8, prostaglandin E2, and matrix metalloproteinases through the stimulation of epithelial, endothelial, and fibroblastic cells. IL-17 appears to be inadequate to mount a potent inflammatory response by itself, but in combination with Th-1 and Th-17 cytokines it can augment or enhance their responses by several fold. The various biological effects of IL-17 on other cytokines are as follows:

- **Monocytes/macrophages:** Production of cytokine-TNF-α, IL-1, NO, PGE2
- **T-cells:** IL-17 production
- **Neutrophils:** Progenitor differentiation, cytokine and chemokine production, maturation, activation
- **Osteoblasts/osteoclasts:** Cytokine production, differentiation, induction of RANKL, activation and maturation, matrix destruction, and matrix synthesis inhibition

**Table 1: Effects of interleukin-17 on cell populations present in the human body**

| IL-17 and its effects on cell populations: |
|----------------------------------------|
| - Monocytes/macrophages: Production of cytokine-TNF-α, IL-1, NO, PGE2 |
| - T-cells: IL-17 production |
| - Neutrophils: Progenitor differentiation, cytokine and chemokine production, maturation, activation |
| - Osteoblasts/osteoclasts: Cytokine production, differentiation, induction of RANKL, activation and maturation, matrix destruction, and matrix synthesis inhibition |

**Flow Chart 1:** Protocol for the identification of studies for review writing
collaboration and/or synergism with other inflammatory cytokines, it accelerates the inflammation. IL-17 can induce a potent inflammatory cascade by increasing the expression of target genes. IL-8 release is functionally important for neutrophil recruitment. IL-6 increases the release of elastase from human neutrophils in vitro. IL-17 shares transcriptional pathways with IL-1 and tumor necrosis factor alpha. p38 and nuclear factor κB are the key transcriptional factors for IL-17 function. IL-17 induces the production and release of colony-stimulating factors (CSFs) granulocyte and granulocyte-macrophage CSFs. Both CSFs are powerful anti-apoptotic survival factors for neutrophils.

**Effect of Interleukin-17 on Systemic Diseases**

IL-17 has been associated with the pathogenesis of different types of systemic inflammatory disorders such as rheumatoid arthritis, psoriasis, systemic sclerosis, systemic lupus erythematosus and bowel disease. It has been observed that the IL-17 level is increased in systemic lupus erythematosus patients. IL-17 plays a crucial role in host defense within the lungs by the stimulation of local release of neutrophil-mobilizing factors in resident cells.

**Role of Interleukin-17 in Periodontitis**

The initiation and progression of periodontal disease depends on complex interactions between periodontal bacteria and cells of immune system. Studies have demonstrated that a number of pro-inflammatory cytokines are released in response to periodontal bacteria and their toxin products. Andrukhov et al. suggested that due to differences in the bacterial profile in periodontitis can be associated with different cytokine profiles.

It is generally acknowledged that control of the Th1/Th2 balance is central to the immunoregulation of periodontal disease. It has been suggested that stable periodontal lesions are mediated by Th1 cells and progression of periodontitis reflects a shift towards Th2 cells and therefore, the pathogenesis of periodontitis is clinically considered as involving Th1/Th2 pattern. However, recently, studies have found that significantly increase in the level of IL-17 in periodontitis condition. IL-17 is found in high amounts in periodontal disease. IL-17 aggravates periodontal disease by activating gingival fibroblasts to produce inflammatory cytokines. There is abundant documentation that suggest major tissue destruction in periodontitis which results from the recruitment of host cells through the activation of monocytes/macrophages, lymphocytes, and fibroblasts. IL-17 is more frequently detected in periodontitis patients than in gingivitis patients. Takahashi et al. have suggested that IL-17 is produced in periodontitis, which may be involved in Th1 modulation and which increase inflammatory reactions through gingival fibroblast-derived mediators and thus, IL-17 has a potential role in the pathogenesis of the periodontal disease. IL-17 has an action on alveolar bone cells. It has been documented that T-cells can be directly involved in bone metabolism through T-cell-derived cytokines which includes IL-17. IL-17 has the ability to stimulate osteoclast cells and activate receptor activator of nuclear factor kappa-B ligand production by osteoblasts.

AgP is generally seen in teenagers and young adult. It is the most severe form of periodontitis which can lead to significant periodontal inflammation and premature tooth loss in maximum number of cases at early age. There is abundant literature suggesting aberrant polymorphonuclear leukocytes (PMN) function as a key pathogenic mechanism in AgP exhibiting defective PMN chemotactic response and enhanced oxidative metabolic responses. Evidence suggest that the rate of bone destruction is about the three to four times faster than in chronic periodontitis. Early age of onset is one of the main characteristics features of AgP; however, patients with AgP are clinically healthy. The amount of microbial deposits is inconsistent with disease severity and the presence of familial aggregation has been reported. IL-17 may play a significant role in AgP because of the functional impairment of PMN and because of the association of IL-17 pathways with the recruitment of neutrophils which results in enhanced inflammation and bone resorption. It has been hypothesized that IL-17 has a key role in regulating neutrophils in vivo and neutrophils play a crucial role in controlling periodontal infection. Neutrophils are considered as the first line of defense against a broad range of periodontal pathogens. Functionally intact neutrophils are necessary for defense in any inflammatory condition. Patients suffering from defects in neutrophils function suffer from recurrent and severe infection including AgP. Neutrophils are also potentially harmful if turned against host tissue. The constant phases of neutrophil mobilization are key components of innate immunity contributing to host defense. Fossiez et al. have suggested that IL-17 activates the mobilization and de novo generation of neutrophils by granulocyte-CSFs, thereby bridging innate and adaptive immunity. IL-17 is important for neutrophil homeostasis and therefore for periodontal health. Any alteration from normal neutrophil activity (in
terms of numbers or activation status) can potentially cause periodontitis.\(^{[64,65]}\) The functional pathways of the IL-17 cells in periodontitis are still not sufficiently understood, and thus, more research is required.

There is abundance literature available with IL-17 levels in chronic periodontitis but miniscule information with IL-17 in relation to AgP cases. More studies in all ethnic groups are necessary which can be used in the development of individualized diagnostic and treatment plans of periodontitis, especially in case of AgP.

**CONCLUSION**

Periodontitis is multifactorial in nature. It is initiated by microorganisms and perhaps viruses and further affected by factors such as diet, smoking, stress, and environmental factors. It is also influenced by acquired systemic diseases which reduce or alter host response. Apart from this, the genetic factor can also be responsible for susceptibility to periodontitis.\(^{[1]}\)

IL-17 plays an important role in periodontitis, but it shows some variations in the levels with respect to chronic periodontitis and AgP. This may be due to different microbiological profiles in periodontitis and defects in neutrophil actions in AgP. Further investigations with larger populations are needed to clarify the specific contribution of IL-17 in the immunopathology of AgP and chronic periodontitis. This will help for anti-IL-17 intervention in periodontitis cases and also to determine the predictive value (cutoff) of IL-17 levels in periodontitis for the diagnostic purpose. Anti-IL-17 intervention for systemic inflammatory conditions such as for rheumatoid arthritis, psoriasis, and ankylosing spondylitis as have already been performed.\(^{[66-70]}\)

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Chaplin DD 1. Overview of the human immune response. J Allergy Clin Immunol 2006;117:S430-5.
2. Gemmell E, Seymour GJ. Cytokines and T cell switching. Crit Rev Oral Biol Med 1994;5:249-79.
3. Wankhede AN, Wankhede SA, Wasu SP. Role of genetic in periodontal disease. J Int Clin Dent Res Organ 2017;9:53-8.
4. Remick DG, Friedland JS, editors. Quantitation of cytokines. In: Cytokines in Health and Disease. (Revised and Expanded). 2nd ed. New York: Marcel Dekker, Inc.; 1997. p. 281-98.
5. Balkwill FR, Burke F. The cytokine network. Immunol Today 1989;10:299-304.
6. Honda T, Domon H, Okui T, Kajita K, Amanuma R, Yamazaki K. Balance of inflammatory response in stable gingivitis and progressive periodontitis lesions. Clin Exp Immunol 2006;144:35-40.
7. Nisenberg RC, Newman MG, Sanz M. Host Response: Basic Concepts. Clinical Periodontology. 8th ed. Philadelphia: W.B. Saunders Co.; 1995. p. 188.
8. Morley J. Prostaglandins and lymphokines in arthritis. Prostaglandins 1974;8:315-26.
9. Medzhitov R. Recognition of microorganisms and activation of the immune response. Nature 2007;449:819-26.
10. Bickel M, Axtelius B, Soloz C, Attström R. Cytokine gene expression in chronic periodontitis. J Clin Periodontol 2001;28:840-7.
11. Yetkin Ay Z, Sütçi R, Uskun E, Bozkurt FY, Berker E. The impact of the IL-11:IL-17 ratio on the chronic periodontitis pathogenesis: A preliminary report. Oral Dis 2009;15:93-9.
12. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol 1986;136:2348-57.
13. Romagnani S. Human TH1 and TH2 subsets: Doubt no more. Immunol Today 1991;12:256-7.
14. Zhao L, Zhou Y, Xu Y, Sun Y, Li L, Chen W. Effect of non-surgical periodontal therapy on the levels of Th1/Th1/Th2 cytokines and their transcription factors in Chinese chronic periodontitis patients. J Clin Periodontal 2011;38:509-16.
15. Belardelli F, Ferrantini M. Cytokines as a link between innate and adaptive antitumor immunity. Trends Immunol 2002;23:201-8.
16. Rouvier E, Luciani MF, Mattéi MG, Denizot F, Golstein P. CTLA-8, cloned from an activated T cell, bearing AU-rich messenger RNA instability sequences, and homologous to a Herpesvirus saimiri gene. J Immunol 1993;150:5445-56.
17. Fossiez F, Djossou O, Chomarat P, Flores-Romo L, Ait-Yahia S, Maat C, et al. T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. J Exp Med 1996;183:2539-603.
18. Aggarwal S, Gurney AL. IL-17: Prototype member of an emerging cytokine family. J Leukoc Biol 2002;71:1-8.
19. Gaffen SL. Structure and signalling in the IL-17 receptor family. Nat Rev Immunol 2009;9:556-67.
20. Ruddy MJ, Wong GC, Liu XK, Yamamoto H, Kasayama S, Kirkwood KL, et al. Functional cooperation between interleukin-17 and tumor necrosis factor-alpha is mediated by CCAAT/enhancer-binding protein family members. J Biol Chem 2004;279:2559-67.
21. Iwakura Y, Ishigame H, Saijo S, Nakae S. Functional specialization of interleukin-17 family members. Immunity 2011;34:149-62.
22. Gu C, Wu L, Li X. IL-17 family: Cytokines, receptors and signaling. Cytokine 2013;64:477-85.
23. Miossec P. Interleukin-17 in rheumatoid arthritis: If T cells were to contribute to inflammation and destruction through synergy. Arthritis Rheum 2003;48:594-601.
24. Toh ML, Gonzales G, Koenders MI, Tournadre A, Boyle D, Lubberts E, et al. Role of interleukin 17 in arthritis chronicity through survival of synoviocytes via regulation of synoviolin expression. PLoS One 2010;5:e13416.
25. Doreau A, Belot A, Bastid J, Riche B, Trescol-Biemont MC, Ranchin B, et al. Interleukin 17 acts in synergy with B cell-activating factor to influence B cell biology and the pathophysiology of systemic lupus erythematosus. Nat Immunol 2009;10:778-85.
26. Griffin GK, Newton G, Tarrio ML, Bu DX, Maganto-Garcia E, Azcutia V, et al. IL-17 and TNF-α sustain neutrophil recruitment
during inflammation through synergistic effects on endothelial activation. J Immunol 2012;188:6287-99.

27. Onishi RM, Gaffen SL. Interleukin-17 and its target genes: Mechanisms of interleukin-17 function in disease. Immunology 2010;129:311-21.

28. Painitia MK, Painitia AS, Singh AK, Singh I. Synergistic activity of interleukin-17 and tumor necrosis factor-α enhances oxidative stress-mediated oligodendrocyte apoptosis. J Neurochem 2011;116:508-21.

29. Ruddy MJ, Shen F, Smith JB, Sharma A, Gaffen SL. Interleukin-17 regulates expression of the CXC chemokine LIX/CXCL5 in osteoblasts: Implications for inflammation and neutrophil recruitment. J Leukoc Biol 2004;76:135-44.

30. Kawaguchi M, Kokubu F, Kuga H, Matsukura S, Hoshino H, Ieki K, et al. Modulation of bronchial epithelial cells by IL-17. J Allergy Clin Immunol 2001;108:804-9.

31. Lindén A. Increased interleukin-8 release by beta-adrenoceptor activation in human transformed bronchial epithelial cells. Br J Pharmacol 1996;119:402-6.

32. Saba S, Soong G, Greenberg S, Prince A. Bacterial stimulation of epithelial G-CSF and GM-CSF expression promotes PMN survival in CF airways. Am J Respir Cell Mol Biol 2002;27:561-7.

33. Van bezooijen RL, Farh-Sips HC, Papapoulos SE, Löwik CW. Interleukin-17: A new bone acting cytokine in vitro. J Bone Miner Res 1999;14:1513-21.

34. Shih DQ, Targin SR, McGovern D. Recent advances in IBD pathogenesis: Genetics and immunobiology. Curr Gastroenterol Rep 2008;10:568-75.

35. Crispin JC, Ouksa M, Bayliss G, Cohen RA, Van Beck CA, Stillman E, et al. Expanded double negative T cells in patients with systemic lupus erythematous produce IL-17 and infiltrate the kidneys. J Immunol 2008;181:8761-6.

36. Wong CK, Lit LC, Tam LS, Li EK, Wong PT, Lam CW, et al. Hyperproduction of IL-23 and IL-17 in patients with systemic lupus erythematosus: Implications for Th17-mediated inflammation in auto-immunity. Clin Immunol 2008;127:385-93.

37. Crispin JC, Tsokos GC. Interleukin-17-producing T cells in lupus. Curr Opin Rheumatol 2010;22:499-503.

38. Lindén A, Laan M, Anderson GP. Neutrophils, interleukin-17A and lung disease. Eur Respir J 2005;25:159-72.

39. Schroeder HE, Münzel-Pedrazzoli S, Page R. Correlated morphometric and biochemical analysis of gingival tissue in early chronic gingivitis in man. Arch Oral Biol 1973;18:899-923.

40. Meikle MC, Heath JK, Reynolds JJ. Advances in understanding cell interactions in tissue resorption. Relevance to the pathogenesis of periodontal diseases and a new hypothesis. J Oral Pathol 1986;15:239-50.

41. Page RC. The role of inflammatory mediators in the pathogenesis of periodontal disease. J Periodontal Res 1991;26:230-42.

42. Kinane DF. Periodontitis modified by systemic factors. Ann Periodontol 1999;4:54-64.

43. Aarvak T, Chabaud M, Miossec P, Navtig JB. IL-17 is produced by some proinflammatory Th1/Th0 cells but not by Th2 cells. J Immunol 1999;162:1246-51.

44. Andrukhov O, Ulm C, Reischl H, Nguyen PQ, Matejka M, Rausch-Fan X. Serum cytokine levels in periodontitis patients in relation to the bacterial load. J Periodontol 2011;82:885-92.

45. Orozco A, Gemmell E, Bickel M, Seymour GI. Interleukin 18 and periodontal disease. J Dent Res 2007;86:586-93.

46. Cardoso CR, Garlet GP, Crippa GE, Rosa AL, Júnior WM, Rossa MA, et al. Evidence of the presence of T helper type 17 cells in chronic lesions of human periodontal disease. Oral Microbiol Immunol 2009;24:1-6.

47. Seymour GJ. Invited review: Possible mechanisms involved in the immunoregulation of chronic inflammatory periodontal disease. J Periodontol Res 1987;66:2-9.

48. Seymour GJ. Importance of the host response in the periodontium. J Clin Periodontol 1991;18:421-6.

49. Saglie FR, Pertuiset J, Rezende MT, Nestor M, Marfany A, Cheng J. In situ correlated immuno-identification of mononuclear infiltrates and invasive bacteria in diseased gingiva. J Clin Periodontol 1988;59:688-96.

50. Oda T, Yoshiie H, Yamazaki K. Porphyromonas gingivalis antigen preferentially stimulates T cells to express IL-17 but not receptor activator of NF-kappaB ligand in vitro. Oral Microbiol Immunol 2003;18:30-6.

51. Takahashi K, Azuma T, Motohira H, Kinane DF, Kitetsu S. The potential role of interleukin-17 in the immunopathology of periodontal disease. J Clin Periodontol 2005;32:369-74.

52. Kong YY, Yoshida H, Sarosi I, Tan HL, Timms E, Capparelli C, et al. OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. Nature 1999;397:315-23.

53. Takayanagi H, Ogawara K, Hida S, Chiba T, Murata S, Sato K, et al. T-cell-mediated regulation of osteoclastogenesis by signalling cross-talk between RANKL and IFN-gamma. Nature 2000;408:600-5.

54. Sato K, Suematsu A, Okamoto K, Yamaguchi A, Morishita Y, Kadono Y, et al. Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction. J Exp Med 2006;203:2673-82.

55. Kotake S, Udagawa N, Takahashi N, Matsuzaki K, Itoh K, Ishiyama S, et al. IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. J Clin Invest 1999;103:1345-52.

56. Schenken HA, Van Dyke TE. Early-onset periodontitis: Systemic aspects of etiology and pathogenesis. Periodontol 2000 1994;6:7-25.

57. Tonetti MS, Mombelli A. Early-onset periodontitis. Ann Periodontol 1999;4:39-53.

58. Ay ZY, Yilmaz G, Özdem M, Koçak H, Sütçü R, Uskun E, et al. The gingival crevicular fluid levels of interleukin-11 and interleukin-17 in patients with aggressive periodontitis. J Periodontol 2012;83:1425-31.

59. Ibbotson GC, Doug C, Kaur J, Gill V, Ostrovsky L, Fairhead T, et al. Functional alpha4-integrin: A newly identified pathway of neutrophil recruitment in critically ill septic patients. Nat Med 2001;7:465-70.

60. Shiohara M, Gombart AF, Sekiguchi Y, Hidaka E, Ito S, Yamazaki T, et al. Phenotypic and functional alterations of peripheral blood monocytes in neutrophil-specific granule deficiency. J Leukoc Biol 2004;75:190-7.

61. Terregino CA, Lubkin CL, Thom SR. Impaired neutrophil adherence as an early marker of systemic inflammatory response syndrome and severe sepsis. Ann Emerg Med 1997;29:400-3.

62. Meddows-Taylor S, Pendle S, Tiemessen CT. Altered expression an immof CD88 and associated impairment of complement 5a-induced neutrophil responses in hummodedeficiency virus type 1-infected patients with and without pulmonary tuberculosis. J Infect Dis 2001;183:662-5.

63. Fossiez F, Banchereau J, Murray R, Van Kooten C, Garrone P, Lebecque S. Interleukin-17. Int Rev Immunol 1998;16:541-51.

64. Darveau RP. Periodontitis: A polymicrobial disruption of host
homeostasis. Nat Rev Microbiol 2010;8:481-90.

65. Hajishengallis E, Hajishengallis G. Neutrophil homeostasis and periodontal health in children and adults. J Dent Res 2014;93:231-7.

66. Baeten D, Baraliakos X, Braun J, Sieper J, Emery P, van der Heijde D, et al. Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: A randomised, double-blind, placebo-controlled trial. Lancet 2013;382:1705-13.

67. Chiricozzi A, Krueger JG. IL-17 targeted therapies for psoriasis. Expert Opin Investig Drugs 2013;22:993-1005.

68. Genovese MC, Durez P, Richards HB, Supronik J, Dokoupilova E, Mazurov V, et al. Efficacy and safety of secukinumab in patients with rheumatoid arthritis: A phase II, dose-finding, double-blind, randomised, placebo controlled study. Ann Rheum Dis 2013;72:863-9.

69. Hueber W, Sands BE, Lewitzky S, Vandemeulebroecke M, Reinish W, Higgins PD, et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn’s disease: Unexpected results of a randomised, double-blind placebo-controlled trial. Gut 2012;61:1693-700.

70. Kellner H. Targeting interleukin-17 in patients with active rheumatoid arthritis: Rationale and clinical potential. Ther Adv Musculoskelet Dis 2013;5:141-52.