Chinese Medical Journal®

Blocking tumor necrosis factor paved the way for targeted therapeutics in inflammatory diseases

Cong-Qiu Chu

Division of Arthritis and Rheumatic Diseases, Oregon Health & Science University and Rheumatology Section, VA Portland Health Care System, Portland, OR 97239, USA.

Tumor necrosis factor (TNF) becomes a well-known name largely owing to the success of its antagonists in therapy of inflammatory diseases.[1,2] In 1975, in searching for cancer therapeutic agent, Lloyd Old and colleagues[3] found a substance in the serum of mice received endotoxin and bacillus Calmette-Guérin infection, which can cause tumor necrosis in experimental tumor models. The substance was named TNF. The gene of TNF was later cloned and proved to be identical to a molecule called cachectin[4] which was responsible for the cachectic status of patients with malignancy. Soon after its protein was purified, TNF was recognized to be a potent inflammatory cytokine[5,6] mediating a wide range of inflammatory activities in the body, but may have a little effect on direct tumor cell killing. The tumor necrosis effect of TNF is actually an indirect action, that is, TNF induces inflammation leading to hemorrhagic necrosis of tumor tissue. Attempts for tumor therapy with TNF has been disappointing, but blocking TNF activity can reduce the toxicity and may enhance the therapeutic effect of immune check point inhibitors. Thereby, combination of TNF and immune checkpoint blockade may be a viable strategy for cancer immunotherapy.[7]

For a while TNF was called TNF-α, when lymphotoxin (LT), a TNF related molecule with tumor necrosis activity was referred to as TNF-β.[8] However, this was short-lived. The name change for TNF was protested as inappropriate since TNF and LT share only 28% similarity at protein level.[9] In 1993, a second member of LT family was discovered and named LTβ, and the prototype LT was referred to as LTα.[10] In the 7th International Congress on TNF-Related Cytokines (held May 17–21, 1998, Hyannis, MA, USA), the term, "TNF-β" was abandoned, naturally, "TNF-α" became a term which is no longer meaningful. Therefore, the term of "TNF" has been reinstated and this has been reflected in the databases of HUGO Gene Nomenclature Committee[11] and International Universal Protein Resource.[12] However, "TNF-α" has still been used in numerous published papers.[13] For reduction of confusion in the literature, I urge authors to use the original name, TNF for this cytokine, as has been done by many other authors in their publications.

TNF is the first cytokine to be successfully targeted for treatment of rheumatoid arthritis (RA)[1] and Crohn disease (CD).[2] TNF inhibitors (TNFi) have been medications prescribed by physicians in daily practice for treating various inflammatory diseases. The success of TNF blockade in chronic inflammatory disease was built on the failure of treatment of sepsis and septic shock. The first two TNF inhibitors, infliximab and etanercept were initially produced for clinical trials for patients with septic shock.[14-16] Unfortunately, blocking TNF activities did not achieve the expected therapeutic effect in those patients with sepsis.[14,15] It was fortunate for patients with RA and those with CD where TNF was identified to be a therapeutic target as it is highly expressed in the synovial tissue in RA[17] and in the submucosal tissue in CD.[18] Five TNFi, namely infliximab, golimumab, adalimumab, certolizumab pegol and etanercept, and their biosimilars are in the market for management of patients with RA. The pivotal role of TNF in the pathogenesis of RA has been proved by the high efficacy of TNFi not only in clinical trials but also in real world patient care.[19,20] The efficacy of other potent biological agents has been compared with that of TNFi to inform recommendations for management of RA in guidelines.[21] A similar efficacy rate of TNFi has been achieved in inflammatory bowel diseases (IBD) to improve the health outcome and reduce the need for surgical intervention.[22-24] TNFi are also effective to treat extra-intestinal manifestations of IBD.[25,26]

TNFi include therapeutic monoclonal antibodies and a fusion protein consisting of extracellular domains of type 2 TNF receptor and human IgG1 Fc fragment. In general,

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001846

Correspondence to: Prof. Cong-Qiu Chu, Division of Arthritis and Rheumatic Diseases, Oregon Health & Science University and Rheumatology Section, VA Portland Health Care System, Portland, OR 97239, USA
E-Mail: chuc@ohsu.edu

Copyright © 2021 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2021;134(21)

Received: 02-07-2021 **Edited by:** Li-Shao Guo

these TNFi have similar therapeutic and adverse effect profiles, but difference exists between these TNFi. The most notable one is etanercept which is ineffective in treating IBD or non-infective uveitis.[27,28] All of these TNFi are able to neutralize activity of soluble TNF and transmembrane TNF to exert their inhibition effect. Etanercept, but not other TNFi, also binds LTα and LTβ and block their activities.[28] For cells bearing transmembrane TNF, antibody mediated cytotoxicity and complement mediated cytotoxicity may take place *in vivo* in TNFi treatment.[27,28] In addition, reverse signaling via transmembrane TNF may also involve in killing of TNF producing cells.[27,28] The subtle difference in mechanism of action of these TNFi has reflected in management of patients with inflammatory diseases. It is not uncommon that a patient might fail to respond to one but will respond to another TNFi.[29]

TNF was also highly expressed in the site of inflammatory tissue, sacroiliac joints[30] in patients with ankylosing spondylitis (AS), suggesting involvement of TNF in the pathogenesis of AS. Inspired by the success in RA and CD, the first randomized control single-centered study with infliximab in spondyloarthritis (SpA) patients was conducted in 2000 after promising results were achieved from two open labeled trials.[31-33] Significant clinical improvement was observed as soon as two weeks after the first dose of infliximab infusion, along with significant reduction of C-reactive protein.[33] The magnitude of therapeutic effect of infliximab in these initial trials of patients with AS or SpA is comparable to that seen in RA patients. Numerous subsequent clinical trials affirmed the therapeutic effects of infliximab and other TNFi and demonstrated a high efficacy in treating AS and SpA[34] as measured by various clinical disease activity assessments. Moreover, treatment of TNFi for AS and SpA has become a disease modifying therapy for those patients. TNFi can slow down the progression of spondylitis and protect patients from neo-ossification in patients on long-term treatment.[35,36] It must be noted that the long-term structural protection effect is demonstrated only in those patients who have been on continuation of TNFi for more than 4 years.[35,36] The benefit has translated in patients in real-world observational studies.[37,38] As seen in RA patients, TNFi have demonstrated benefit in reducing disability and cardiovascular complications in SpA patients.[39]

The success of TNF blockade in treating inflammatory diseases has become a model for developing targeted therapy and set a high bar for subsequent development of targeted therapy in inflammatory diseases. For instance, clinical improvement by blocking interleukin-17 (IL-17) therapy for RA did not reach the magnitude of TNF blockade, thereby was considered to be a failure.[40,41] However, IL-17 blockade has become a second class of highly efficacious biological therapeutics for patients with SpA. Despite the inferior therapeutic effect to TNFi in RA, IL-17 inhibition has been extremely potent in treating psoriasis and has been effective in SpA.[42] Antibodies to IL-17A or a dual specific antibody (bimekizumab) to IL-17A and IL-17F have clearly shown the superiority over placebo in SpA patients in both TNFi-naïve and TNFi-experienced cohorts.[43-47] The clinical efficacy of TNFi and IL-17 inhibitors (IL-17i) appear to be similar for treating SpA patients, but it is not possible to state which is superior since there are no head-to-head comparative data available. Interestingly, observational studies showed in axial spondylitis (axSpA) patients who failed prior TNFi had comparable responsiveness to secukinumab versus an alternative TNFi.[48,49] Since syndesmophyte formation is a slow process, whether IL-17i have significant suppressive effect on new bone formation will need long-term observations to determine. Enthesitis is an important comorbidity in SpA patients but is only recently recognized. Therapeutic effect of enthesitis by IL-17i have been assessed (mainly in patients with psoriatic arthritis). Limited data in clinical trials demonstrated effectiveness of IL-17i versus placebo.[50,51] Intriguingly, ustekinumab, a monoclonal antibody to the common subunit, p40 of IL-12 and IL-23, was shown to be superior to TNFi in treating peripheral enthesitis although it has no effect in treating axSpA.[52] Currently, TNFi and IL-17i are the only effective targeted biological drugs for SpA. Switching between TNFi and IL-17i will become a common practice. Studies have shown that alternate TNFi have similar effect to IL-17i in patients who failed prior TNFi. It would be interesting to know whether patients who failed an IL-17i will respond to a TNFi. Since they block different inflammatory pathways, it needs head-to-head trials to determine whether TNFi are superior to IL-17i and vice versa. It would also be interesting to investigate whether a synergistic therapeutic effect can be achieved between TNFi and IL-17i.

TNF blockade has become the gold standard in treating many inflammatory diseases in assessing the efficacy of novel targeted therapeutic agents as in the case of IL-17i and Janus kinase (JAK) inhibitors. Furthermore, TNFi have also been a reference for safety assessment for JAK inhibitors.

Funding

Dr. Chu's work was supported by an Innovative Award from American College of Rheumatology Research Foundation and by a VA Merit Review grant (No. I01BX005195).

References

1. Elliott MJ, Maini RN, Feldmann M, Kalden JR, Antoni C, Smolen JS, *et al*. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet 1994;344:1105–1110. doi: 10.1016/s0140-6736(94)90628-9.
2. Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, *et al*. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med 1997;337:1029–1035. doi: 10.1056/NEJM199710093371502.
3. Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson B. An endotoxin-induced serum factor that causes necrosis of tumors. Proc Natl Acad Sci U S A 1975;72:3666–3670. doi: 10.1073/pnas.72.9.3666.
4. Beutler B, Greenwald D, Hulmes JD, Chang M, Pan YC, Mathison J, *et al*. Identity of tumour necrosis factor and the macrophage-secreted factor cachectin. Nature 1985;316:552–554. doi: 10.1038/316552a0.
5. Old LJ. Tumor necrosis factor. Sci Am 1988;258 5:59–60. 69-75. doi: 10.1038/scientificamerican0588-59.

6. Old LJ. Tumor necrosis factor (TNF). Science 1985;230:630–632. doi: 10.1126/science.2413547.
7. Perez-Ruiz E, Minute L, Otano I, Alvarez M, Ochoa MC, Belsue V, *et al*. Prophylactic TNF blockade uncouples efficacy and toxicity in dual CTLA-4 and PD-1 immunotherapy. Nature 2019;569:428–432. doi: 10.1038/s41586-019-1162-y.
8. Shalaby MR, Aggarwal BB, Rinderknecht E, Svedersky LP, Finkle BS, Palladino MA Jr. Activation of human polymorphonuclear neutrophil functions by interferon-gamma and tumor necrosis factors. J Immunol 1985;135:2069–2073.
9. Ruddle NH. Activation of human polymorphonuclear neutrophil functions by interferon-gamma and tumor necrosis factors. J Immunol 1986;136:2335–2336.
10. Browning JL, Ngam-ek A, Lawton P, DeMarinis J, Tizard R, Chow EP, *et al*. Lymphotoxin beta, a novel member of the TNF family that forms a heteromeric complex with lymphotoxin on the cell surface. Cell 1993;72:847–856. doi: 10.1016/0092-8674(93)90574-a.
11. Committee HGN. TNF. https://wwwgenenamesorg/tools/search/#!/?query=TNF.
12. UniProt. TNF. https://wwwuniprotorg/uniprot/?query=TNF&sort=score.
13. Grimstad O. Tumor necrosis factor and the tenacious alpha. JAMA Dermatol 2016;152:557. doi: 10.1001/jamadermatol.2015.4322.
14. Abraham E. Why immunomodulatory therapies have not worked in sepsis. Intensive Care Med 1999;25:556–566. doi: 10.1007/s001340050903.
15. Vilcek J. From IFN to TNF: a journey into realms of lore. Nat Immunol 2009;10:555–557. doi: 10.1038/ni0609-555.
16. Fisher CJ Jr, Agosti JM, Opal SM, Lowry SF, Balk RA, Sadoff JC, *et al*. Treatment of septic shock with the tumor necrosis factor receptor: Fc fusion protein. The Soluble TNF Receptor Sepsis Study Group. N Engl J Med 1996;334:1697–1702. doi: 10.1056/NEJM199606273342603.
17. Chu CQ, Field M, Feldmann M, Maini RN. Localization of tumor necrosis factor alpha in synovial tissues and at the cartilage-pannus junction in patients with rheumatoid arthritis. Arthritis Rheum 1991;34:1125–1132. doi: 10.1002/art.1780340908.
18. Murch SH, Braegger CP, Walker-Smith JA, MacDonald TT. Location of tumour necrosis factor alpha by immunohistochemistry in chronic inflammatory bowel disease. Gut 1993;34:1705–1709. doi: 10.1136/gut.34.12.1705.
19. Aaltonen KJ, Ylikyla S, Tuulikki Joensuu J, Isomaki P, Pirila L, Kauppi M, *et al*. Efficacy and effectiveness of tumour necrosis factor inhibitors in the treatment of rheumatoid arthritis in randomized controlled trials and routine clinical practice. Rheumatology (Oxford) 2017;56:725–735. doi: 10.1093/rheumatology/kew467.
20. Zink A, Strangfeld A, Schneider M, Herzer P, Hierse F, Stoyanova-Scholz M, *et al*. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials. Arthritis Rheum 2006;54:3399–3407. doi: 10.1002/art.22193.
21. Kerschbaumer A, Sepriano A, Smolen JS, van der Heijde D, Dougados M, van Vollenhoven R, *et al*. Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis 2020;79:744–759. doi: 10.1136/annrheumdis-2019-216656.
22. Sokol H, Seksik P, Cosnes J. Complications and surgery in the inflammatory bowel diseases biological era. Curr Opin Gastroenterol 2014;30:378–384. doi: 10.1097/MOG.0000000000000078.
23. Kim NH, Jung YS, Moon CM, Lee SY, Kim ER, Kim YH, *et al*. Long-term clinical outcomes of korean patient with Crohn's disease following early use of infliximab. Intest Res 2014;12:281–286. doi: 10.5217/ir.2014.12.4.281.
24. Chudy-Onwugaje KO, Christian KE, Farraye FA, Cross RK. A state-of-the-art review of new and emerging therapies for the treatment of IBD. Inflamm Bowel Dis 2019;25:820–830. doi: 10.1093/ibd/izy327.
25. Colombel JF, Schwartz DA, Sandborn WJ, Kamm MA, D'Haens G, Rutgeerts P, *et al*. Adalimumab for the treatment of fistulas in patients with Crohn's disease. Gut 2009;58:940–948. doi: 10.1136/gut.2008.159251.
26. Generini S, Giacomelli R, Fedi R, Fulminis A, Pignone A, Frieri G, *et al*. Infliximab in spondyloarthropathy associated with Crohn's disease: an open study on the efficacy of inducing and maintaining remission of musculoskeletal and gut manifestations. Ann Rheum Dis 2004;63:1664–1669. doi: 10.1136/ard.2003.012450.
27. Billmeier U, Dieterich W, Neurath MF, Atreya R. Molecular mechanism of action of anti-tumor necrosis factor antibodies in inflammatory bowel diseases. World J Gastroenterol 2016;22 42:9300–9313. doi: 10.3748/wjg.v22.i42.9300.
28. Mitoma H, Horiuchi T, Tsukamoto H, Ueda N. Molecular mechanisms of action of anti-TNF-alpha agents - comparison among therapeutic TNF-alpha antagonists. Cytokine 2018;101:56–63. doi: 10.1016/j.cyto.2016.08.014.
29. Manica SR, Sepriano A, Pimentel-Santos F, Gouveia N, Barcelos A, Branco JC, *et al*. Effectiveness of switching between TNF inhibitors in patients with axial spondyloarthritis: is the reason to switch relevant? Arthritis Res Ther 2020;22:195. doi: 10.1186/s13075-020-02288-8.
30. Braun J, Bollow M, Neure L, Seipelt E, Seyrekbasan F, Herbst H, *et al*. Use of immunohistologic and in situ hybridization techniques in the examination of sacroiliac joint biopsy specimens from patients with ankylosing spondylitis. Arthritis Rheum 1995;38:499–505. doi: 10.1002/art.1780380407.
31. Brandt J, Haibel H, Cornely D, Golder W, Gonzalez J, Reddig J, *et al*. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab. Arthritis Rheum 2000;43:1346–1352. doi: 10.1002/1529-0131(200006)43:6<1346::AID-ANR18>3.0.CO;2-E.
32. Van den Bosch F, Kruithof E, Baeten D, De Keyser F, Mielants H, Veys EM. Effects of a loading dose regimen of three infusions of chimeric monoclonal antibody to tumour necrosis factor alpha (infliximab) in spondyloarthropathy: an open pilot study. Ann Rheum Dis 2000;59:428–433. doi: 10.1136/ard.59.6.428.
33. Van Den Bosch F, Kruithof E, Baeten D, Herssens A, de Keyser F, Mielants H, *et al*. Randomized double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor alpha (infliximab) versus placebo in active spondylarthropathy. Arthritis Rheum 2002;46:755–765. doi: 10.1002/art.511.
34. Maxwell LJ, Zochling J, Boonen A, Singh JA, Veras MM, Tanjong Ghogomu E, Benkhalti Jandu M, Tugwell P, Wells GA. TNF-alpha inhibitors for ankylosing spondylitis. Cochrane Database Syst Rev 2015;CD005468. doi: 10.1002/14651858.CD005468.pub2.
35. Karmacharya P, Duarte-Garcia A, Dubreuil M, Murad MH, Shahukhal R, Shrestha P, *et al*. Effect of therapy on radiographic progression in axial spondyloarthritis: a systematic review and meta-analysis. Arthritis Rheumatol 2020;72:733–749. doi: 10.1002/art.41206.
36. Ajrawat P, Touma Z, Sari I, Taheri C, Diaz Martinez JP, Haroon N. Effect of TNF-inhibitor therapy on spinal structural progression in ankylosing spondylitis patients: a systematic review and meta-analysis. Int J Rheum Dis 2020;23:728–743. doi: 10.1111/1756-185X.13829.
37. Koo BS, Oh JS, Park SY, Shin JH, Ahn GY, Lee S, *et al*. Tumour necrosis factor inhibitors slow radiographic progression in patients with ankylosing spondylitis: 18-year real-world evidence. Ann Rheum Dis 2020;79:1327–1332. doi: 10.1136/annrheumdis-2019-216741.
38. Sepriano A, Ramiro S, Wichuk S, Chiowchanwisawakit P, Paschke J, van der Heijde D, *et al*. Tumor necrosis factor inhibitors reduce spinal radiographic progression in patients with radiographic axial spondyloarthritis: a longitudinal analysis from the alberta prospective cohort. Arthritis Rheumatol 2021;73:1211–1219. doi: 10.1002/art.41667.
39. Atzeni F, Nucera V, Galloway J, Zoltan S, Nurmohamed M. Cardiovascular risk in ankylosing spondylitis and the effect of anti-TNF drugs: a narrative review. Expert Opin Biol Ther 2020;20:517–524. doi: 10.1080/14712598.2020.1704727.
40. Blanco FJ, Moricke R, Dokoupilova E, Codding C, Neal J, Andersson M, *et al*. Secukinumab in active rheumatoid arthritis: a phase III randomized, double-blind, active comparator- and placebo-controlled study. Arthritis Rheumatol 2017;69:1144–1153. doi: 10.1002/art.40070.
41. Genovese MC, Greenwald M, Cho CS, Berman A, Jin L, Cameron GS, *et al*. A phase II randomized study of subcutaneous ixekizumab, an anti-interleukin-17 monoclonal antibody, in rheumatoid arthritis patients who were naive to biologic agents or had an inadequate response to tumor necrosis factor inhibitors. Arthritis Rheumatol 2014;66:1693–1704. doi: 10.1002/art.38617.

42. Chu CQ. Targeting the IL-17 pathway in inflammatory disorders. Gewerbestrasse, Switzerland: Springer International Publishing AG; 2017.
43. Baeten D, Sieper J, Braun J, Baraliakos X, Dougados M, Emery P, *et al*. Secukinumab, an Interleukin-17A inhibitor, in ankylosing spondylitis. N Engl J Med 2015;373:2534–2548. doi: 10.1056/NEJMoa1505066.
44. Pavelka K, Kivitz A, Dokoupilova E, Blanco R, Maradiaga M, Tahir H, *et al*. Efficacy, safety, and tolerability of secukinumab in patients with active ankylosing spondylitis: a randomized, double-blind phase 3 study, MEASURE 3. Arthritis Res Ther 2017;19:285. doi: 10.1186/s13075-017-1490-y.
45. Sieper J, Deodhar A, Marzo-Ortega H, Aelion JA, Blanco R, Jui-Cheng T, *et al*. Secukinumab efficacy in anti-TNF-naive and anti-TNF-experienced subjects with active ankylosing spondylitis: results from the MEASURE 2 Study. Ann Rheum Dis 2017;76:571–592. doi: 10.1136/annrheumdis-2016-210023.
46. van der Heijde D, Cheng-Chung Wei J, Dougados M, Mease P, Deodhar A, Maksymowych WP, *et al*. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. Lancet 2018;392:2441–2451. doi: 10.1016/S0140-6736(18)31946-9.
47. van der Heijde D, Gensler LS, Deodhar A, Baraliakos X, Poddubnyy D, Kivitz A, *et al*. Dual neutralisation of interleukin-17A and interleukin-17F with bimekizumab in patients with active ankylosing spondylitis: results from a 48-week phase IIb, randomised, double-blind, placebo-controlled, dose-ranging study. Ann Rheum Dis 2020;79:595–604. doi: 10.1136/annrheumdis-2020-216980.
48. Glintborg B, Lindstrom U, Di Giuseppe D, Provan SA, Gudbjornsson B, Hetland ML, *et al*. One-year treatment outcomes of secukinumab versus tumor necrosis factor inhibitors in Spondyloarthritis. Arthritis Care Res (Hoboken) 2020. published ahead of print. Nov 30. doi: 10.1002/acr.24523.
49. Micheroli R, Tellenbach C, Scherer A, Burki K, Niederman K, Nissen MJ, *et al*. Effectiveness of secukinumab versus an alternative TNF inhibitor in patients with axial spondyloarthritis previously exposed to TNF inhibitors in the Swiss Clinical Quality Management cohort. Ann Rheum Dis 2020;79:1203–1209. doi: 10.1136/annrheumdis-2019-215934.
50. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, *et al*. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015;386:1137–1146. doi: 10.1016/S0140-6736(15)61134-5.
51. Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, *et al*. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis 2017;76:79–87. doi: 10.1136/annrheumdis-2016-209709.
52. Araujo EG, Englbrecht M, Hoepken S, Finzel S, Kampylafka E, Kleyer A, *et al*. Effects of ustekinumab versus tumor necrosis factor inhibition on enthesitis: results from the enthesial clearance in psoriatic arthritis (ECLIPSA) study. Semin Arthritis Rheum 2019;48:632–637. doi: 10.1016/j.semarthrit.2018.05.011.

How to cite this article: Chu CQ. Blocking tumor necrosis factor paved the way for targeted therapeutics in inflammatory diseases. Chin Med J 2021;134:2525–2528. doi: 10.1097/CM9.0000000000001846