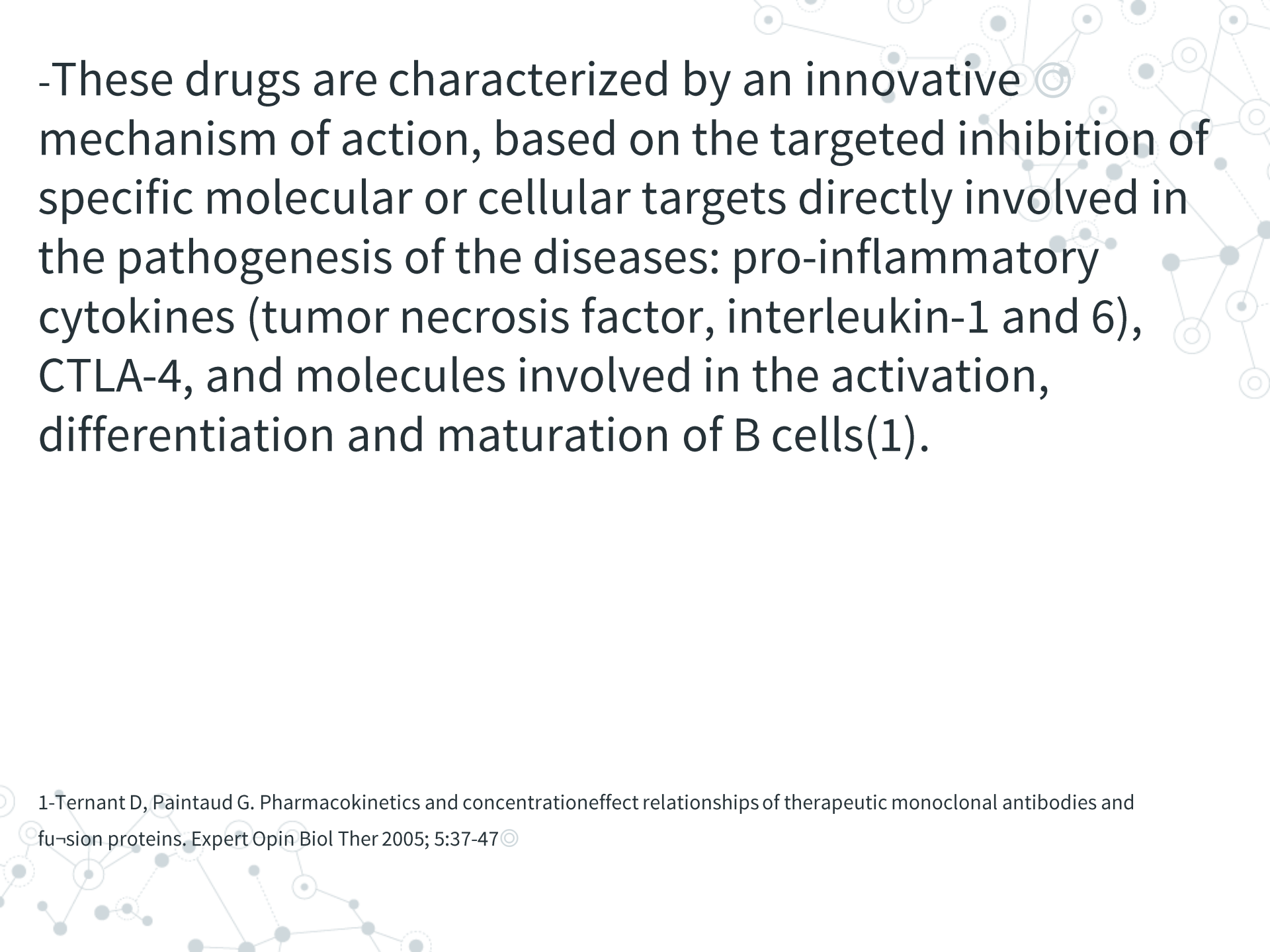


Biological therapies in rheumatic diseases

Dr.M KUDSI

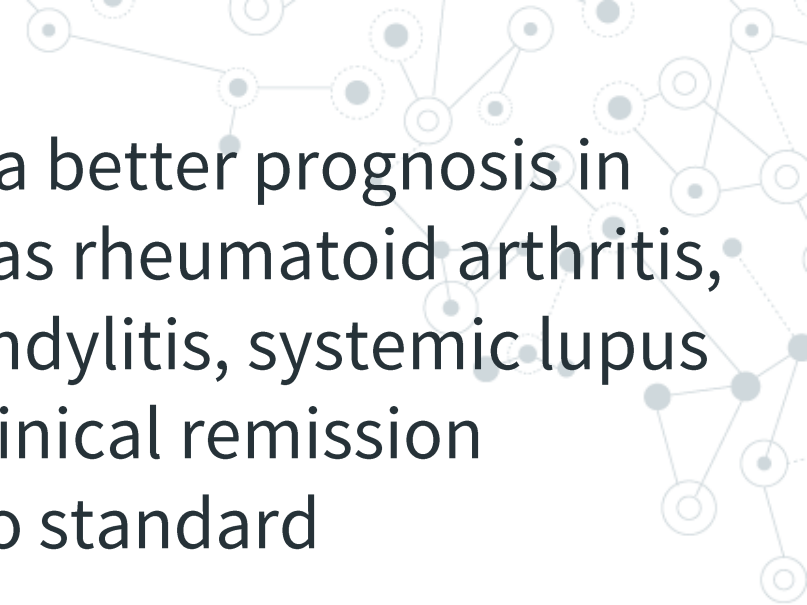
Dmascus University





-These drugs are characterized by an innovative mechanism of action, based on the targeted inhibition of specific molecular or cellular targets directly involved in the pathogenesis of the diseases: pro-inflammatory cytokines (tumor necrosis factor, interleukin-1 and 6), CTLA-4, and molecules involved in the activation, differentiation and maturation of B cells(1).

1-Ternant D, Paintaud G. Pharmacokinetics and concentrationeffect relationships of therapeutic monoclonal antibodies and fu-sion proteins. Expert Opin Biol Ther 2005; 5:37-47



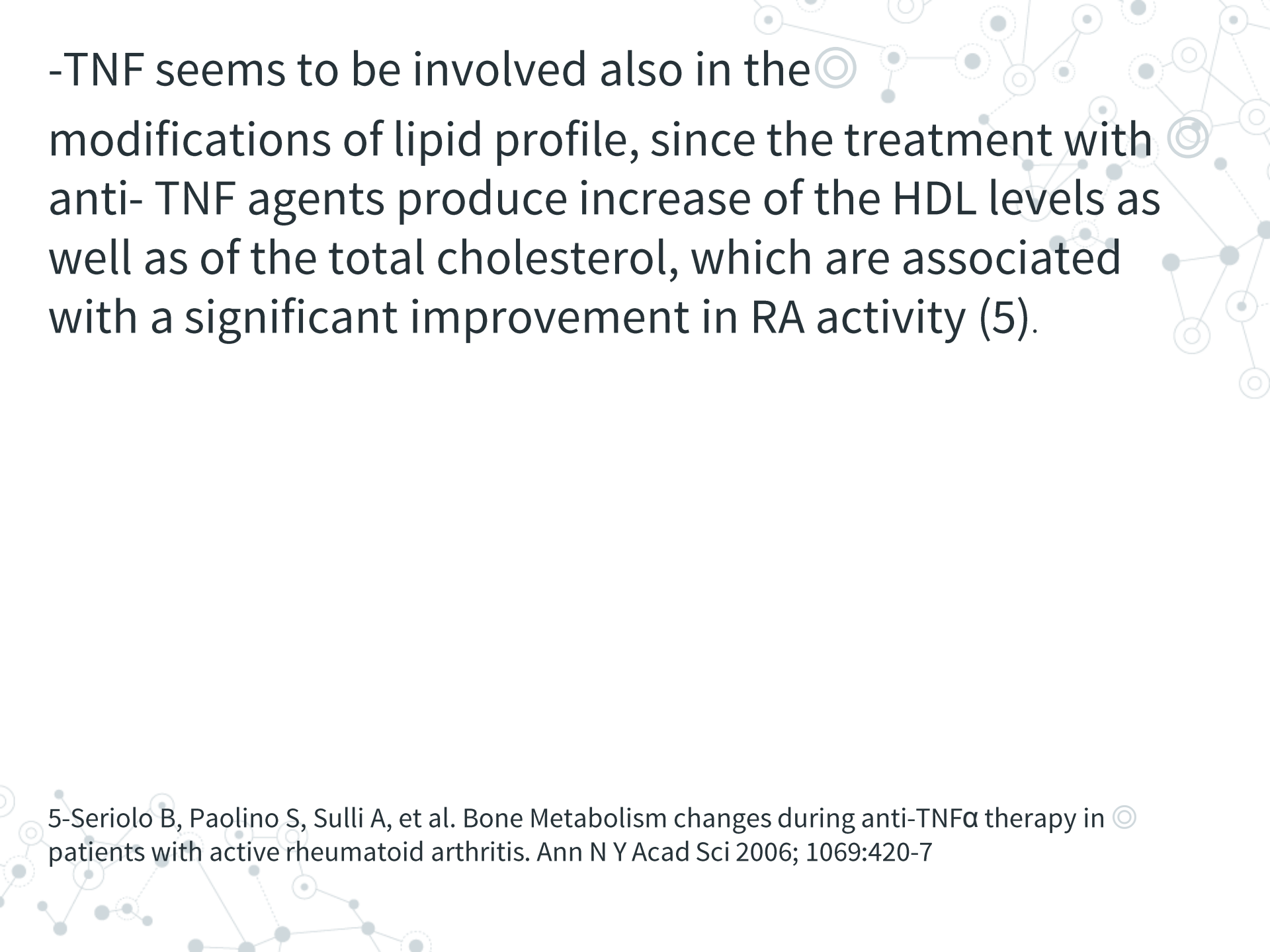
-Their use has indeed allowed for a better prognosis in several rheumatic diseases (such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus) and to obtain a clinical remission particularly in patients resistant to standard treatment(2).

TNF antagonists

- The mechanism of action of TNF antagonists is based on the neutralization of both sTNF and mTNF.
- The interruption of the signal pathways mediated by TNF has numerous consequences, reflecting the pleiotropic effect of the cytokine cell cycle arrest, apoptosis, inhibition of pro-inflammatory cytokine and chemokine release, but also of chondrocyte, osteoclast, and endothelial cell activation, reduction of leukocyte accumulation and angiogenesis, increase of T reg cell number(3,4).

3-Caporali R, Bobbio Pallavicini F, Filippini M, et al. Treatment of rheumatoid arthritis with anti-TNF-alpha agents: A reappraisal. Autoimmun Rev 2008; 8:274-80.

4-Ulfgren AK, Andersson U, Engstrom M, et al. Systemic anti-tumor necrosis factor alpha therapy in rheumatoid arthritis down-regulates synovial tumor necrosis factor alpha synthesis. Arthritis Rheum 2000; 43:2391-6



-TNF seems to be involved also in the modifications of lipid profile, since the treatment with anti- TNF agents produce increase of the HDL levels as well as of the total cholesterol, which are associated with a significant improvement in RA activity (5).

5-Seriolo B, Paolino S, Sulli A, et al. Bone Metabolism changes during anti-TNF α therapy in patients with active rheumatoid arthritis. Ann N Y Acad Sci 2006; 1069:420-7

Approved indications



Rheumatoid arthritis

Main randomized controlled trials testing the efficacy of anti-TNF agents in RA patients.

| Study | Treatment | T. Duration | Outcom◎ |
|--------------------------|----------------------------|-------------|--|
| COMET, Emery(6) | ETA + MTX vs MTX | 52 weeks | Remission (DAS28), radiographic progression◎ |
| TEMPO, Klareskog(7) | ETA + MTX vs ETA or MTX | 52 weeks | ACR response, radiographic progression◎ |
| ERA, Genovese(8) | ETA vs MTX | 12 months | ACR response, radiographic progression◎ |
| ATTRACT, Maini (9) | IFX + MTX vs MTX | 30 weeks | ACR response◎ |
| ASPIRE, St. Claire (10) | IFX + MTX vs MTX | 54 weeks | ACR response, radiographic progression◎ |
| ARMADA, Weinblatt (11) | ADA + MTX vs MTX | 24 weeks | ACR response◎ |
| PREMIER, Breedveld (12) | ADA + MTX vs ADA or MTX | 2 years | ACR response, radiographic progression◎ |
| GO-AFTER, Smolen (13) | GLM50.100mg ± vs DMARDs v | 24 weeks | ACR response HAQ-DI, DAS28 remission◎ |
| GO-FORWARD, Keystone(14) | GLM50,100mg + vs MTX\P | 52 weeks | ACR response, DAS28, safety |
| RAPID-1, Keystone (15) | CZP400+MTXvsCZP200+MTXvsMT | 52 weeks | ACR response; radiographic progression◎ |

- 
- 6-Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis, (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 2008; 82:372:5
- 7- Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment. *Lancet* 2004; 363:675-81
- 8-Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2002; 6:1443-50
- 9- Maini R, St Clair EW, Lipsky, et al. Infliximab (chimeric anti-tumor necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomized phase III trial. *Lancet* 1999;9-354-8.
- 10-St Clair EW, van der Heijde DM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004; 50:3432-43.
- 11-Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003; 48:35-45
- 12-Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 37-1:2006.
- 13-Smolen JS, Kay J, Doyle MK, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet* 2009; 374:210-21.
- 14-Keystone E, Genovese MC, Klareskog L, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. *Ann Rheum Dis* 2010; 69:1129-35.
- 15-Keystone E, van der Heijde D, Mason D, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis. *Arthritis Rheum* 2008; 58:3319-29-

Spondyloarthritis:

-PsA and AS are the two entities with the most severe course of all SpAs, and several RCT testing TNF antagonists have been run in such patients demonstrating an impressive clinical efficacy, with no specific superiority in terms of efficacy of one of them over the others(16).

16-Glintborg B, Ostergaard M, Krogh NS, et al. Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor:results from 8 years' surveillance in the Danish nationwide DANBIO registry. Ann Rheum Dis 2010; 69:2002-8

Main randomized controlled trials testing the efficacy of anti-TNF agents in AS and PsA patients.

| Study | Treatment | T.duration | Outcome |
|------------------------|--------------------------|------------|---|
| Braun (17)As | IFX vs placebo | 12 weeks | BASDAI, BASFI, BASMI, SF-36 |
| ASSERT(18) AS | IFX vs placebo | 24 weeks | ASAS response, BASDAI, BASFI, BASMI, SF-36, CRP |
| Davis (19) AS | ETA vs placebo | 24 weeks | ASAS response, safety |
| van der Heijde (20) AS | ADA vs placebo | 24 weeks | ASAS response, BASDAI, BASFI, BASMI, CRP, SJC, TJC |
| GO-RAISE (21) AS | GLM 50,100 mgvs placebo | 24 weeks | ASAS response, BASDAI, BASFI, BASMI, SF-36 |
| IMPACT(22) PsA | IFX vs placebo | 50 weeks | ACR response, PASI, DAS28, HAQ |
| HAQ(23) PsA | ETA vs placebo | 12 weeks | ACR response, PsARC, PASI |
| Mease (24) PsA | ADA vs placebo | 24 weeks | ACR response, radiographic progression (modified Sharp score), PsARC, PASI, HAQ,SF-36 |
| GO-REVEAL(25)PsA | GLM 50,100 mg vs placebo | 24 weeks | ACR response,PASI,SF-36 |

17-Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet* 2002; 359:1187-93

18-van der Heijde D, Dijkmans B, Geusens P et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum* 2005; 52:582-591

19-Davis JC Jr, van der Heijde D, Braun J, et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized controlled trial. *Arthritis Rheum* 2003; 48:3230-6.

20-van der Heijde D, Kivitz A, Schiff MH, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006; 54:2136-41.

21-Inman RD, Davis JC Jr, van der Heijde D, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. *Arthritis Rheum* 2008; 58:3402-12

22-Antoni CE, Kavanaugh A, Kirkham B, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). *Arthritis Rheum* 2005; 52:1227-36

23-Mease PJ, Goffe BS, Metz J, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet* 2000; 356:3585

24-Mease PJ, Gladmann DD, Ritchlin CT, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005; 52:3279-89


25-Kavanaugh A, McInnes I, Mease P, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 2009;60-86.

Anti-IL-1 agents


-IL-1 α mainly acts in an autocrine fashion and partially by exerting a paracrine function, which result in local inflammation.

Conversely, IL-1 β is released into the circulation and stimulates systemic inflammation.

-The two receptors mediating their action, IL-1RI and IL-1RII, are expressed on the macrophages and B lymphocyte surfaces as a membrane receptor and also released in a soluble form(26).



-The binding of IL-1 to its receptor initiates the recruitment of several kinases with development of the pro-inflammatory cascade(27).



27-Dinarello Ca, Simon A, van der Meer JWM. Treating inflammation by blocking interleukine-1 in a broad spectrum of diseases. Nature Rev 2012; 11:633-52

Approved indications◎

Rheumatoid arthritis: ◎


-Anakinra, alone or in combination with MTX, resulted ◎
effective in the reduction of disease activity and damage
and in the improvement of the quality
of life (28).◎

-After 16 weeks of treatment with anakinra, a ◎
significant improvement in signs, symptoms and ◎
laboratory parameters, as well as a slowing of
radiographic progression, was registered in RA patients
(29).


28-Fleishmann RM, Schechtman J, Bennett R, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist (rmetHull-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. Arthritis◎

Rheum 2003; 48:927-34◎

29-Rubbert-Roth A. Assessing the safety of biologic agents in patients with rheumatoid arthritis. Rheumatology (Oxford)2012;47.◎



-Despite the absence of clinical trials directly comparing anakinra with respect to TNF antagonists, the experience clearly demonstrates a superiority of the TNF blocking strategy in RA(30).

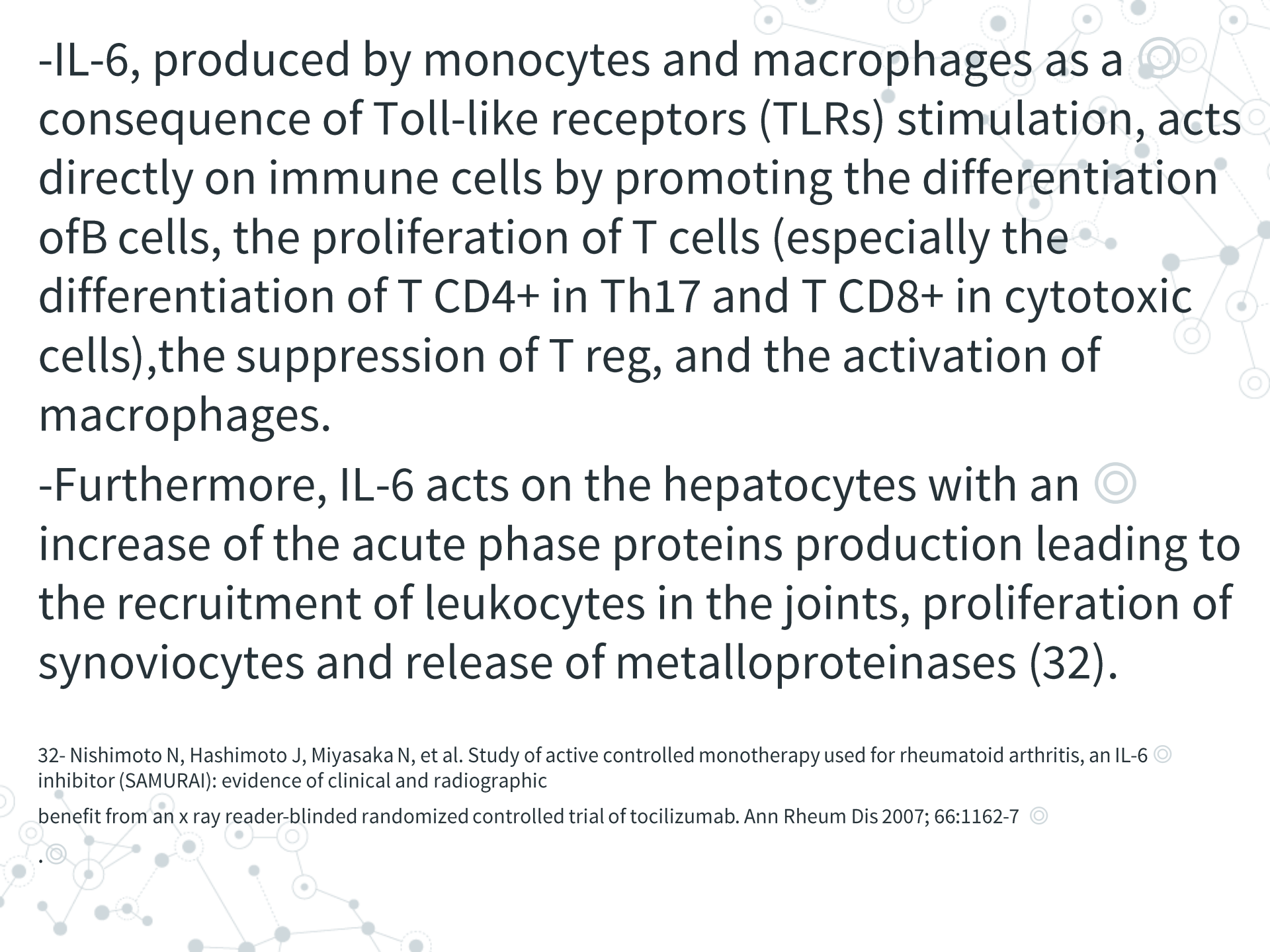


30-Bresnihan B. The safety and efficacy of interleukin-1 receptor antagonist in the treatment of rheumatoid arthritis. Semin Arthritis Rheum 2001; 30, 2:17-20

Anti-IL-6 agent ©

-IL-6 is a pleiotropic cytokine that plays a key role in the inflammatory processes by inducing the activation of several cells involved in immune response.

-It acts by means of interaction with its receptor (IL-6R), composed of two chains. The first chain, formed by a domain containing the binding site for IL-6, could exist in soluble form or associated with(31).



-IL-6, produced by monocytes and macrophages as a consequence of Toll-like receptors (TLRs) stimulation, acts directly on immune cells by promoting the differentiation of B cells, the proliferation of T cells (especially the differentiation of T CD4⁺ in Th17 and T CD8⁺ in cytotoxic cells), the suppression of T reg, and the activation of macrophages.

-Furthermore, IL-6 acts on the hepatocytes with an increase of the acute phase proteins production leading to the recruitment of leukocytes in the joints, proliferation of synoviocytes and release of metalloproteinases (32).

32- Nishimoto N, Hashimoto J, Miyasaka N, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic

benefit from an x ray reader-blinded randomized controlled trial of tocilizumab. Ann Rheum Dis 2007; 66:1162-7

- The IL-6 effects on osteoblasts, endothelial and mesangial cells, fibroblasts and keratinocytes determine the cartilage and subchondral bone degradation and loss of systemic bone.
- Moreover, an increase of the collagen synthesis was reported, contributing to skin changes that occur in psoriasis and systemic sclerosis (33).

- High concentrations of IL-6 demonstrated in serum and synovial fluid of patients affected by RA. In the synovial fluid the IL-6/IL-6R complex induces the formation of osteoma-like cells and in bone marrow induces the activation of the RANK/RANKL complex.
- Moreover, IL-6 increases the production of VEGF that results in an increase of angiogenesis and of the synovial permeability(34).

34-Grossman RM, Krueger J, Yourish D, et al. Interleukin-6 is expressed in high levels in psoriatic skin and stimulates proliferation of cultured human keratinocytes. Proc Natl Acad Sci U S A 1989; 86:6367-71.

Approved indications◎

RA ◎

- Patients with moderate/severe disease activity, both as first-line therapy after failure of DMARDs, or after the failure of TNF inhibitors (33).
- The response to treatment with tocilizumab is ◎ comparable to that of other biologics in terms of ACR response .Particularly, in the SAMURAI study, tocilizumab has proven effective in reducing joint damage (34).

Main randomized controlled trials testing the efficacy of tocilizumab in RA patients.

| Study | Treatment | T. duration | outcomes |
|---|---------------------------------|-------------|--------------------------------|
| SAMURAI, Nishimoto (32) (modified Sharp score), ACR response, DAS, HAQ | TCZ vs DMARDs | 52 weeks | Radiographic progression, |
| AMBITION, Jones (35) | TCZ vs MTX | 24 weeks | ACR response, HAQ, DAS28 |
| OPTION, Smolen (33) 36,FACIT-F | TCZ4,8 mg + MTX vs MTX | 24 weeks | ACR response, DAS28, HAQ, SF- |
| SATORI, Nishimoto (36) levels | TCZ vs MTX | 24 weeks | ACR response, DAS28, HAQ, VEGF |
| CHARISMA, Maini (37) levels | TCZ 2 mg/4 mg/8 mg ± MTX vs MTX | 20 weeks | ACR response, DAS28, CRP/ESR |

35-Jones G, Sebba A, Gu J et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis 2010; 69:88-96.

36-Nishimoto N, Miyasaka N, Yamamoto K, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to metotrexate(SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol 2009; 19:12-19.

37-Maini RN, Taylor PC, Kishimoto J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, Tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum 2006; 6:2817-29

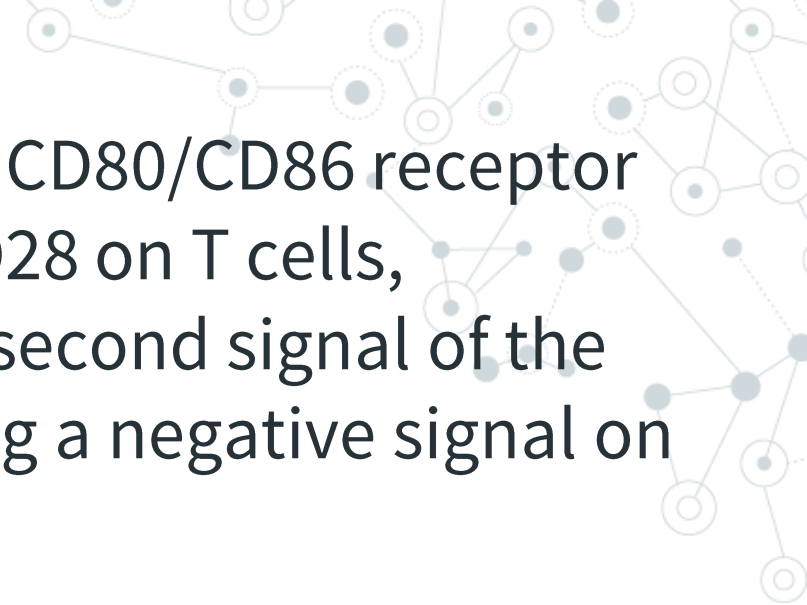
Co-stimulation signal blockade

-At the beginning, the block of the T cells activation was experimented to act directly on CD28. Unfortunately, the administration of an antibody against CD28 in healthy volunteers evoked a cytokine storm associated with multiorgan

failure (38).◎

-Thus, efforts have been focused on enhancing the inhibitory action of CTLA-4.◎

Abatacept is a selective modulator of the CD80/86-CD28 co-stimulatory signal, essential for activation of T cells.◎



-It blocks specific binding of the CD80/CD86 receptor in antigen presenting cells to CD28 on T cells, inhibiting the transmission of a second signal of the immune response, and producing a negative signal on T cell activation (39).

Rheumatoid arthritis: ©

- Moderate/severe disease activity that do not respond to treatment with conventional DMARDs or anti-TNF.
- Abatacept can be administered in combination with DMARDs(40).

40-Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med 2005; 353:1114-23 ©

Main randomized controlled trials testing the efficacy of abatacept in RA patients.

| Study | Treatment | T.duration | Outcomes |
|--------------|------------------------------|-------------------|---|
| ATTAIN(40) | Abatacept vs placebo | 6 months | ACR response, HAQ |
| ATTEST(41) | (Abatacept vs IFX) +MTXvsMTX | 6 months | ACR response, EULAR response,HAQ, DAS28, safety |
| AIM(42) | Abatacept + MTX vs MTX | 1 year | ACR response, DAS28,HAQ, SF-36, radiographic progression(Genant-modified Sharp score) |
| ASSURE(43) | Abatacept + DMARDs vsDMARDs | 1 year | Safety |

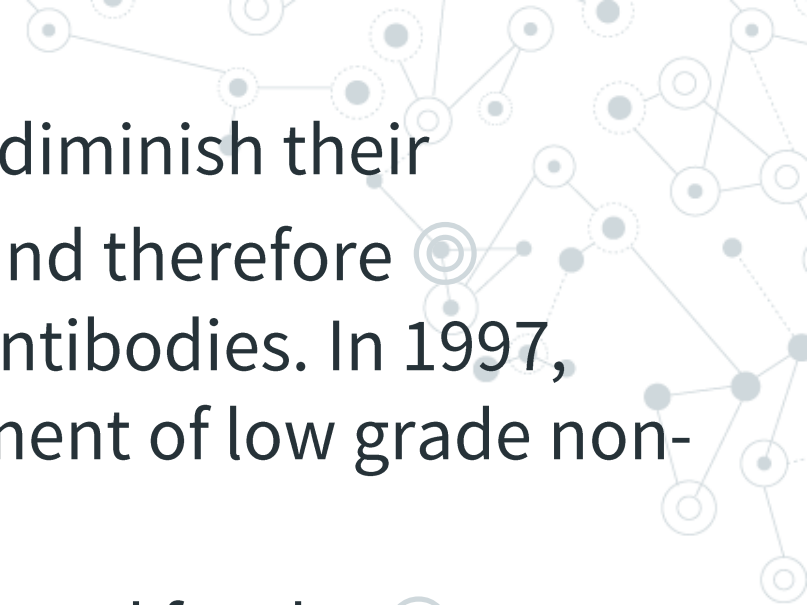
41-Schiff M, Keiserman M, Coddig C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomized, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis 2008; 67:1096-1103.

42-Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med 2006;76-144

43-Weinblatt M, Combe B, Covucci A, et al. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. Arthritis Rheum 2006;16-54.


B-cell-depleting therapy

Rituximab, blocking the CD20, leads to the removal of intermediate stages of B cells. The treatment outcome is a transient but complete depletion of B cells in the blood and a partial depletion of B cells in the bone marrow and synovial tissue.



-The aim in depleting B cells is to diminish their differentiation into plasma cells and therefore decrease the production of autoantibodies. In 1997, approved rituximab for the treatment of low grade non-Hodgkin's B cell lymphomas.

-About ten years later it was approved for the treatment of RA(44).



44-Anolik JH, Barnard J, Cappione A, et al. Rituximab improves peripheral B cell abnormalities in human systemic lupus erythematosus. Arthritis Rheum 2004; 50:3580-90

Main randomized controlled trials testing the efficacy of rituximab in RA patients.

| Study | Treatment | T. duration | Outcomes |
|--|---|-------------|-------------------------------|
| IMAGE,(45) | RTX 2 x 500 ,100mg + MTX vs MTX | 52 weeks | ACR response, EULAR response, |
| DAS28, HAQ, radiographic progression(Genant-modified Sharp) | | | |
| SERENE(46) | RTX 2 x 500,1000 mg + MTXvs MTX | 48 weeks | ACR response, EULAR response, |
| DAS28, HAQ, FACIT-F, SF-36,safety | | | |
| MIRROR(47) | 3 regimens comprising 2 courses of RTX: 2 | 48 weeks | ACR response, DAS28, |
| EULAR response, SF-36,FACIT-F, HAQ, safety | | | |
| SUNRISE(48) | RTX or placebo | 48 weeks | |
| ACR response, DAS28, HAQ,CRP/ESR levels, EULAR response,safety | | | |

45-Tak PP, Rigby WF, Rubbert-Roth A, et al. Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: the IMAGE trial. Ann Rheum Dis 2011; 70:39-46.

46-Emery P, Deodhar A, Rigby WF, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomized, placebo-controlled trial in patients who are biological naïve with active rheumatoid arthritis and an inadequate response to methotrexate. [Study Evaluating Rituximab’s Efficacy in MTX iNadequate rEsponders (SERENE)]. Ann Rheum Dis2010:35-61.

47-Rubbert-Roth A, Tak PP, Zerbini C, et al. Efficacy and safety of various repeat treatment dosing regimens of rituximab in patients with active rheumatoid arthritis: results of a phase III randomized study, MIRROR Rheumatol Oxford 2010;49-93.


48Mease PJ, Cohen S, Gaylis NB, et al. Efficacy and safety of retreatment in patients with rheumatoid arthritis with previous inadequate response to tumor necrosis factor inhibitors: results from the SUNRISE trial. J Rheumatol 2010; 5:917-27-

Off-label use

A decorative network diagram in the top right corner, consisting of various sized circles (nodes) connected by thin lines (edges), some solid and some dashed, creating a complex web-like structure.

Since 2000, rituximab was used to treat SLE patients refractory to conventional treatment producing convincing results in many case series and in uncontrolled trials(49).

49-Ferro D, Pignatelli P, Loffredo L, et al. Soluble CD154 plasma levels in patients with systemic lupus erythematosus: modulation by antiphospholipid antibodies. Arthritis Rheum2004;40-50.

A decorative network diagram in the bottom left corner, similar to the one in the top right, featuring a cluster of nodes and connecting lines.

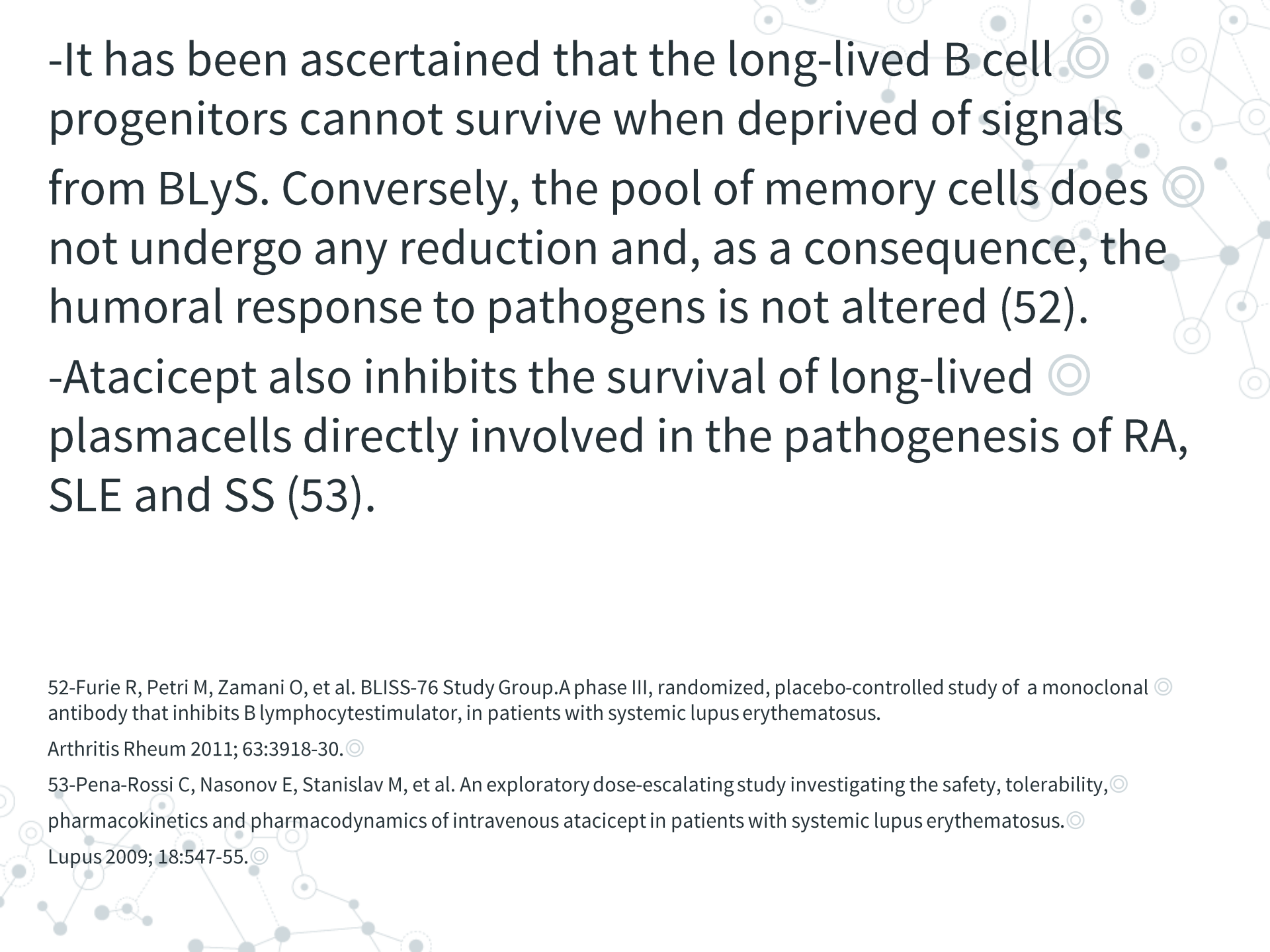
Belimumab ©

- Neutralizes B lymphocyte stimulator (BlyS), a potent B cell survival factor.
- SLE patients have elevated BlyS levels which correlate with their autoantibody titers and disease activity.
- Inhibition of this factor results in apoptosis of © autoreactive B cells.

Atacicept: ©

- This is a recombinant fusion protein comprising the extracellular domain of the TACI© (Transmembrane Activator and CAML Interactor) © receptor joined to a human IgG1 Fc domain.
- It functions mainly by blocking the interaction© between BLyS/APRIL with their receptor TACI© expressed on mature B cells, plasma cells and © activated T cells (51).

51-Pena-Rossi C, Nasonov E, Stanislav M, et al. An exploratory dose-escalating study investigating the safety, tolerability© pharmacokinetics and pharmacodynamics of intravenous atacicept in patients with systemic lupus erythematosus. © Lupus 2009; 18:547-55 ©



-It has been ascertained that the long-lived B cell progenitors cannot survive when deprived of signals from BLyS. Conversely, the pool of memory cells does not undergo any reduction and, as a consequence, the humoral response to pathogens is not altered (52).

-Atacicept also inhibits the survival of long-lived plasmacells directly involved in the pathogenesis of RA, SLE and SS (53).

52-Furie R, Petri M, Zamani O, et al. BLISS-76 Study Group. A phase III, randomized, placebo-controlled study of a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus.

Arthritis Rheum 2011; 63:3918-30.

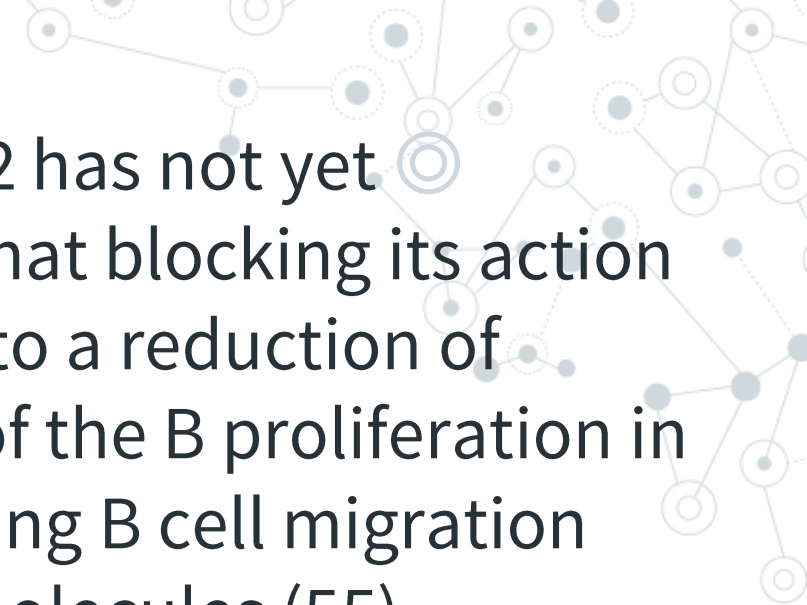
53-Pena-Rossi C, Nasonov E, Stanislav M, et al. An exploratory dose-escalating study investigating the safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous atacicept in patients with systemic lupus erythematosus.

Lupus 2009; 18:547-55.

Epratuzumab: ©

- This is a humanized mAb formed by anIgG1 directed against CD22. CD22 is a lectin-like member of the Ig superfamily solely expressed by mature B cells.
- Its function is to modulate the B cell receptor and © signal transduction through CD19, and participates in mediating signals for survival (54).

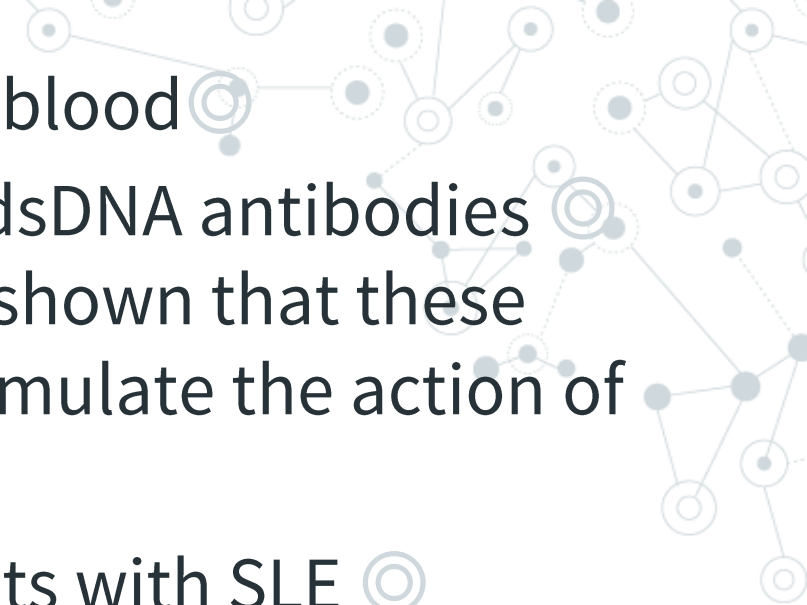
54-Jacobi AM, Goldenberg DM, Hiepe F, et al. Differential effects of epratuzumab on peripheral blood B cells of patients © with systemic lupus erythematosus versus normal controls. Ann Rheum Dis 2008; 67:450-57 ©



-Although the precise role of CD22 has not yet clarified, recent studies suggest that blocking its action with the use of a mAb could lead to a reduction of peripheral B cells and inhibition of the B proliferation in SLE patients, negatively modulating B cell migration and the expression of adhesion molecules (55).

Anti-IFN

- Type I IFN seems to play a central role in the pathogenesis of SLE and is therefore a potential therapeutic target.
- The alterations involve primarily IFN α , maybe due to the presence of specific genetic polymorphisms that affect the production of type I IFN, its activities and serum concentrations(56).



-The immune complexes found in blood of patients with SLE contain anti-dsDNA antibodies and nucleic acids and it has been shown that these immune complexes are able to stimulate the action of IFN.

-In the blood and tissues of patients with SLE numerous IFN-producing cells, and an increase of IFN mRNA and of the IFN itself, were also found.

Sifalimumab: ©

-This is a fully human IgG1k mAb that ©
binds to IFN α with high affinity and prevents IFN α ©
signaling through its receptor. The phase I study on
patients with (SLE) demonstrated a good safety profile
that supports further clinical development.

58-Merrill JT, Wallace DJ, Petri M, et al. Safety profile and clinical activity of sifalimumab, a fully human anti-interferon ©
 α monoclonal antibody in systemic lupus erythematosus: a phase I, multicentre, double-blind randomized study. Ann ©
Rheum Dis 2011; 70:1905-13 ©

Approved indications of the available biologic drugs according to European Medicine Agency (EMA).

| Drug | Approved indications | | | |
|--------------|----------------------|-----|----|-----|
| | RA | PsA | AS | SLE |
| Abatacept | x | | | |
| Adalimumab | x | x | | x |
| Belimumab | x | | | |
| Certolizumab | x | | | |
| Etanercept | x | x | | x |
| Golimumab | x | x | | x |
| Infliximab | x | x | | x |
| Rituximab | x | | | |
| Tocilizumab | x | | | |

Legend: RA: rheumatoid arthritis, PsA: psoriatic arthritis, ◎

AS: ankylosing spondylitis, SLE: systemic lupus erythematosus. ◎

Conclusions

The biological drugs have revolutionized the management of the patients affected by chronic inflammatory rheumatic diseases, allowing a better prognosis and the achievement of clinical remission in a significant percentage of patients.

These drugs target different molecules directly involved in the pathogenesis of several diseases, such as RA, PsA, AS and SLE.

New biological drugs are now under investigation.

QUESTIONS?



<http://go.funpic.hu>