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KATA PENGANTAR

SalamSejawat,

Selamat bertemu kembali di awal tahun ini.Pada saat ini, penyakit autoimun menjadi trending topik di kalangan masyarakat.Sebagai seorang dokter, kita wajib terlibat untuk berkontribusi baik secara edukasi maupun terapi.

Keluhan nyeri sendi dan muskuloskeletal juga banyak dijumpai baik di tempat praktek maupun di rumah sakit.Meskipun telah diperoleh banyak kemajuan dalam pengetahuan tentang patogenesis penyakit reumatik dan nyeri, banyak topik-topik penelitian menunjukkan bahwa sebahagian besar penderita tidak mendapatkan pengobatan yang optimal untuk mengatasi keluhan mereka.

Dengan berkembangnya ilmu pengetahuan dan teknologi di bidang kedokteran terutama Reumatologi, pada kesempatan yang baik ini Divisi Reumatologi Departemen Ilmu Penyakit Dalam FK USU/ RSUP. H. Adam Malik berencana mengawali tahun 2020 dengan mengajak para sejawat bersama-sama untuk berdiskusi secara scientifik pada acara "Rheumatology Update 2020" tentang materi yang hangat di masyarakat dengan mengundang para pakar lain yang berhubungan dengan penyakit reumatik.

Acara ini merupakan kegiatan yang berisi symposium dan workshop injeksi Intra Artikular dan Muskuloskletal dengan para pembicara Nasional serta pemeran farmasi yang nantinya diharapkan akan memberikan kontribusi yang meningkatkan layanan kesehatan masyarakat.

Medan, Januari 2020
Ketua Panitia

Dr. dr. Blondina Marpaung Sp.PD, K-R

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LONG TERM EFFICACY IN ADALIMUMAB FOR RHEUMATOID ARTHRITIS THERAPY

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1. Introduction

Great advances in the treatment of chronic autoimmune inflammatory arthritis, concerning both therapeutic concepts and means, have marked the last two decades. In the 1990s the inversion of the classical "therapeutic pyramid" for the treatment of rheumatoid arthritis (RA) became mainstream in rheumatologypractice,whilelatertheconcept"treatearlytotreateffectively"wasrealizedasanecessity in order to achieve favorable outcomes in RA both in the short and long term. Concerning medications methotrexate (MTX) was regarded as the "anchor drug" for the treatment of RA,while other disease-modifying anti-rheumatic drugs (DMARDs) such as cyclosporine A and leflunomide were recruited or developed to add further therapeutic benefit against chronic inflammatory arthritis as monotherapy or in combination.[1]

Despite the implementation of these new therapeutic concepts and agents there were issues still to be addressed. A considerable proportion of patients with RA could experience no significant benefit: for example in randomized controlled trials in early RA, 35% of patients receiving MTX monotherapy failed to achieve a 20% American College of Rheumatology (ACR) response at year 1 and 44% at year 2.[1]

Ontheotherhand,recentadvancesinmolecularandcellularbiologyshedlightinmechanismsof rheumatic diseases revealing the role of specific molecules, such as tumor necrosis factor-alpha (TNFα), interleukin (IL)-1, IL-6, IL-17, IL-23, immune cell co-stimulation pathways and the role of specific immune cell subsets, such as Th1, Th2, Th17, T regulatory cells, B cells and dendritic cells. Taking advantageofgeneticengineeringtechniquesandthemonoclonalantibodytechnologythenewknowledge led to the development of molecules targeting specific pathogenic cytokines (TNFα, IL-1, IL-6), T-cell co-stimulation pathways associated with the cytotoxic T lymphocyte antigen-4 (CTLA-4) and even B- cells, thus launching the era of targeted therapies inrheumatology.[1]

In PsA and AS anti-TNFα agents have produced satisfactory outcomes, even better than in RA. Long-term data on efficacy are still limited though, while the impact of these drugs on radiographic damage seems to vary with more pronounced effects in peripheral than axial joints. Another issue is the time length of treatment, since there is evidence that cessation of treatment leads to disease relapse.[1] As regardsthesafetyofTNFαblockers,whereasinitialscreeningandahighdegreeofsuspicionhavereduced the occurrence of severe, particularly mycobacterial Infections, the risk of malignancy in the long term is anemergingandstillunresolvedissue.Further,inductionofautoimmunity,neurologicdisease,effectson metabolic parameters and the cardiovascular risk are issues not yet investigatedthoroughly.

2. Adalimumab

Adalimumab is currently indicated for the reduction of signs and symptoms of adults with moderately to severely active RA, despite the use of DMARDs, including MTX; also for MTX-naive adults with severe, active progressing RA. In RA patients, adalimumab may be administered in combination with MTX or without MTX, if the latter is contraindicated or poorly tolerated. Moreover, adalimumab is indicated for the treatment of adults with active progressing DMARD-resistant PsA, as well as adults with severe active AS with a poor response to conventional therapy. It is also indicated, in combinationwithMTXorasmonotherapy(incasesMTXiscontra-indicated)forthetreatmentofsevere activepolyarticularjuvenileidiopathicarthritis(JIA)resistanttoatleastoneDMARD.Therecommended initial dose for all adult indications is 40 mg administered subcutaneously (sc) every other week(qow).

TNFαisacytokinecentraltoacomplexnetworkofcellsandmediatorsoperatingininflammation and in particular in the pathogenesis of chronic inflammatory arthritis: directly or indirectly it promotes migration of inflammatory cells, activates inflammatory and joint parenchymal cells and inducesthe

production and release of other pro-inflammatory cytokines and metalloproteinases propagating the inflammatory process and tissue damage.

Adalimumab is a full-length bivalent monoclonal IgG1-κ antibody with a molecular weight of 150 kD targeting specifically TNFα (both soluble [sTNFα] and membrane-bound (mTNFα]). Developed withaphagedisplaytechniqueandproducedinaChinesehamsterovariancellline,itconsistscompletely of human IgG1-κ sequences and is indistinguishable from human IgG1. It binds 2 sTNFα molecules, having even the potential to form multimeric complexes, thus preventing sTNFα from binding to the natural TNFα receptors (p55/CD120a and p75/CD120b). Alternatively adalimumab binds 2 mTNFα molecules with the potential of cross-linking and reverse intracellular signaling. Adalimumab does not bind lymphotoxin. Adalimumab may thus mediate its actions through various mechanisms: direct neutralization of sTNFα and mTNFα, apoptosis and cytokine suppression through reverse mTNFα-mediated signaling, antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity directed against cells expressing mTNFα (Figure1).

WhengiventopatientswithRA,adalimumabincreasestotalTNFαlevelsprobablyreflectingthe formation of TNFα-adalimumab complexes, reduces p75 and p55 soluble TNF receptor levels, reduces IL-1β mRNA expression, reduces IL-6 and IL-1 receptor antagonist levels, reduces metalloproteinase levels (such as pro-MMP-1, pro-MMP-3, MMP-1, MMP-3), reduces cartilage and synovium turnover markers and increases the percentage of memory CD8+ and CD4+ T cells and CD19+ Bcells.

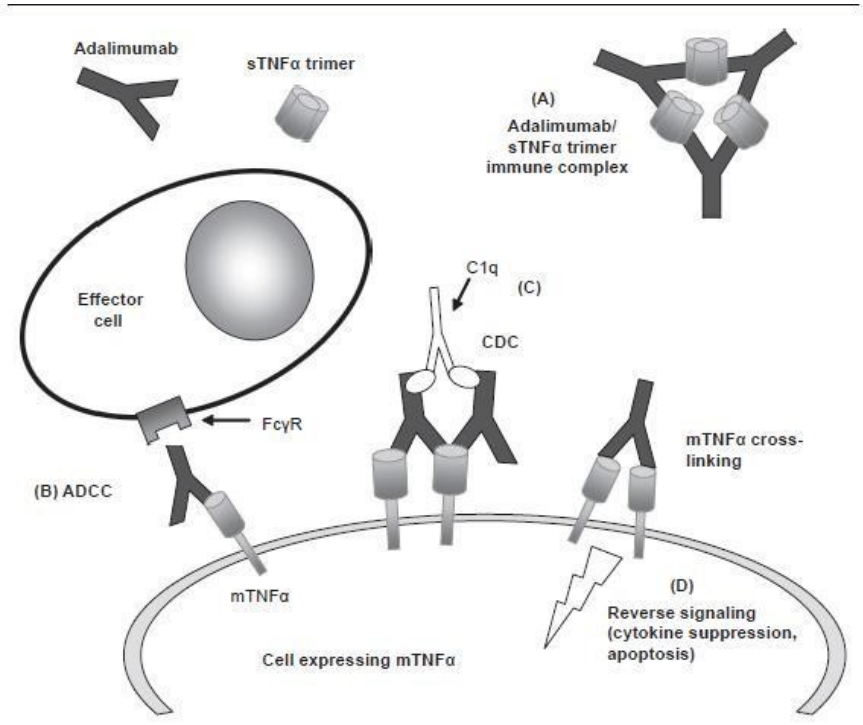

Figure 1 Putative pathways whereby adalimumab exerts its actions. Adalimumab binds to soluble TNFα trimers forming immune complexes (A) thus preventing sTNFα from binding to TNF receptor (TNFR). Alternatively it may bind to mTNFα expressed on cell surface preventing its own binding to TNFR (not shown); or it induces antibody-dependant cell-mediated cytotoxicity (ADCC) via binding to FcγR expressed on the surface of effector cells (B); moreover adalimumab may directly activate complement classical pathway inducing complement-dependant cytotoxicity (CDC), (C); finally, cross-linking of mTNFα may cause reverse signaling leading to cytokine suppression and/or cellular apoptosis (D).

3. Adalimumab for RheumatoidArthritis

Short-term (6 to 12 months) efficacy and safety of adalimumab in RA has been investigated in 5 multicenter randomized controlled trials, 4 of them with established RA one with early RA7 and comprising 2869 patients overall. The results of these trials (summarized by Voulgari an Drosos72) indicate superiority of adalimumab versus placebo or adalimumab in combination with conventional DMARDs versus conventional DMARDs only, in terms of clinical and radiographic efficacy and an acceptable safety profile. The earliest long-term data derive from open-label extension of an initial phase I study. In this study, 59 RA patients with an inadequate response to MTX were given additional adalimumab initially at various doses, and, during the second year, at a dose of 40 mg every other week or monthly and were followed up for overall 26 months. At the end of follow-up almost 60%, 45% and

30% of patients achieved ACR20, ACR50 and ACR70 responses respectively, similar to the response rates achieved at 6 months already (□62%, 42%, 20% respectively).

These preliminary results were confirmed in the extension of the ARMADA trial and of the DE019study,aswellasinthePREMIERstudy.IntheARMADAtrial,271patientswithestablishedRA were randomized to adalimumab 20 mg, 40 mg or 80 mg subcutaneously qow plus MTX or placebo plus MTX for 24 weeks. Of these patients 262 continued in an openlabel extension phase receiving a combination of adalimumab (40 mg qow) plus MTX and were followed up for a maximum of 4 years. Although228,207,186and168patientscompletedyear1,2,3and4ofthestudy,completeclinicaldata wereavailablefor176,196,176and147patientsattherespectivetimepoints.WhereastheACR20/50/70 responseratesoftheadalimumab40mggroupat6monthswere67.2%,55.2%,26.9%respectively,ACR 20/50/70 response rates at year 1 were 78%, 55%, 31%, at year 2 79%, 54%, 33%, at year 3 77%, 58%, 32% and at year 4 78%, 57%, 31% respectively, showing a sustained efficacy of the combination of adalimumab and MTX over 4 years. Furthermore, disease remission (defined as 28 joint count Disease Activity Score [DAS 28] was achieved by 34% of patient at year 1, 38% at year 2 and 3 and 43% at year 4, while mean DAS28 values were 3.2, 3.1, 3.1 and 3.0 at the respective time points. Similarly sustained efficacy was seen as regards joint counts and CRPvalues.

Among patients on corticosteroids more patients were able to reduce the dose or discontinue corticosteroids and only one patient had the corticosteroid dose increased, whereas more patients could reducetheirMTXdosethanincreaseit.MTXandcorticosteroiddosereductionswerenotassociatedwith worsening of the disease activity measures. In the DE019 trial,84 619 patients with established RA refractory to MTX were randomized to receive adalimumab 40 mg qow or adalimumab 20 mg weekly or placebo for one year, while continuing MTX. Patients who had completed the 52-week trial were subsequently eligible for an open-label extension, during which all patients received adalimumab 40 mg qow plus MTX. At 52 weeks ACR20/50/70 response rates in the 40 mg qow group were 58.9%, 41.5% and 23.2% respectively, whereas the respective rates for the placebo group were 24%, 9.5% and 4.5%. For those who completed 5 years of treatment with adalimumab ACR20/50/70, response rates further improved, being 75%, 58% and 35%respectively.

The safety profile of adalimumab in its various indications has been evaluated in several controlled clinical trials and their open-label extensions, in observational studies, through spontaneous reports of adverse events and through biologic drug registries, after the drug had been released in the market.Duringtheshorttimeframeoftheplacebo-controlledclinicaltrialsinRA,AS,PsAandJIA,rates of adverse events in the adalimumab-receiving groups, in most cases, were comparable to the rates observed in the placebogroups

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