Dr Morton Scheinberg

3º Congresso Latino Americano de Autoinmunidad
Buenos Aires, julio-2010
Biologic Therapy for the treatment of Rheumatic Diseases: Where we are and Where we are going.
Biological anti-T/B cell mAb therapies

Tissue cells

B cell

T cell

Mø

DC

TNF
IL-18
IL-1
IL-15
IL-10
IL-6
IL-1
IL-18
IL-15
IL-6
IL-1

TACI
BCMA

IFNα

LJP

CD40L

CD40

CD28

TCR

B7

MHC

FcR

TNF

IL-1

IL-18

IL-15

IL-6

IFNα
New targets? Which targets are we talking about?

- Anti cytokines
- Anti B cell therapy
- Inhibitors of T cell co stimulation
- Anti cell adhesion molecules
- Inhibitors of intracellular signalling
- Others


Mecanismo de Ação

- Mecanismo de Ação
- Modelos Experimentais
- Camundongos Transgenicos
- Ensaios Clinicos
Desenvolvimento de Inibidores de TNF

Monoclonal contra TNF

Monoclonal contra TNF receptors
1998 Infliximab

1998 Etanercept

2003 Adalimumab
TNFα Inhibitors: ACR50 at 1 Year

<table>
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<tr>
<th>Treatment</th>
<th>MTX alone</th>
<th>TNFα inhibitor alone</th>
<th>TNFα inhibitor + MTX</th>
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<tr>
<td>Etanercept</td>
<td>43%</td>
<td>48%</td>
<td>69%</td>
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<tr>
<td>TEMPO (N=682)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration</td>
<td>~7 y</td>
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<tr>
<td>Infliximab</td>
<td>32%</td>
<td>50%</td>
<td>62%</td>
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<tr>
<td>ASPIRE (N=1004)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Disease duration</td>
<td>~0.9 y</td>
<td></td>
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<tr>
<td>Adalimumab</td>
<td>46%</td>
<td>41%</td>
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<tr>
<td>PREMIER (N=799)</td>
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<tr>
<td>Disease duration</td>
<td>~0.7 y</td>
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Disease duration:  
*P≤0.0001 vs MTX alone; †P≤0.001 vs MTX alone.

Efficacy With MTX Alone in Early RA (<3 Years)

ACR

<table>
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<tr>
<td>ERA¹</td>
<td>65</td>
<td>54</td>
<td>42</td>
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<tr>
<td>ASPIRE² — Week 54</td>
<td>63</td>
<td>46</td>
<td>32</td>
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<tr>
<td>PREMIER² — Week 52</td>
<td>54</td>
<td>22</td>
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</table>

Radiographic Progression

Mean change in TSS

0   1   2   3   4   5   6

MTX dose rapidly escalated to 20 mg/week in these studies.
TSS = Total Sharp Score.

Relato de Caso


Metotrexate foi iniciado nas doses de 15mg semanal e como ele não conseguia digitar introduzi 10mg de prednisona diariamente.

Após quatro meses o paciente ao exame apresentava sete articulações dolorosas edemaciadas.
MGV paciente do centro oeste sexo feminino 55 anos de idade AR diagnosticada há sete anos. Vem a São Paulo com quadro de poliartrite em mãos e punhos e cotoveis. Apresenta franca sinovite em ambos os cotoveis erosões na ressonância

Magnética VHS 77mm PCR 46mg/l hemoglobina de 9.8. Funcionaria da CEF. Medicação atual Plaquinol 1x ao dia Metotrexate 17.5mg e Prednisona 20.0mg por dia já a dois anos.

Devemos introduzir um biológico porque e qual?
Por que:
Dois cenários distintos:
Artrite Reumatóide precoce versus tardia
We determined, in our surrounding environment, the proportion of patients being treated with infliximab who required a therapeutic scheme escalation (an infliximab dose increase surpassing the level of 3 mg/kg every 8 weeks and/or a decrease on the current between infusions' interval). This was a study of the retrospective analysis of data from the 41 rheumatoid arthritis (RA) patients receiving an infliximab therapy at the Albert Einstein Israelita Hospital, from January 2001 up to December 2005. A questionnaire was applied to these patients, assessing their clinical and laboratory data, adverse events, and individual information regarding the infliximab administration. Therapeutic dose information was available in 68% (28/41) of the RA patients, with 46% of these (13/28) receiving a dose increase, and 30% (8/27) experiencing a shortening of the between infusions' interval. The average final infliximab dose (4.21 mg/kg) was significantly greater than their average initial dose (3.29 mg/kg). The average time intervals between the initial and final infusions, though shortened, were not significantly different. A proportion of 73% (30/41) of these patients demonstrated improvement in at least one of the assessed clinical parameters, and 50% of these patients (15/30) experienced a dose increase, while 20% (6/30) experienced shortening of the between treatments' interval. A total of 20% (8/41) of the original patients experienced adverse events. Although infliximab is effective in the control of RA, dose adjustment and/or shortening of the between treatments' interval is frequently required.
A melhora clínica em doenças inflamatórias autoimunes com anti TNFs e a ponta do iceberg. Não está relacionada a causa e a recidiva após a suspensão e um bom exemplo deste cenário.
Treatment options in patients with rheumatoid arthritis failing initial TNF inhibitor therapy: a critical review

Andrea Rubbert-Roth1 and Axel Finckh2
Opções Terapêuticas em Falhas de Anti TNF

Switching (eficácia)?

Abatacept em falhas de anti TNF (ATTAIN)

Rituximab em falhas de anti TNF (REFLEX)


Interleukin-6: from basic science to medicine-40 years in immunology.

Kishimoto T
Graduate School of Frontier Bioscience, Osaka University, Osaka 565-0871, Japan.
kishimot@imed3.med.osaka-u.ac.jp

This essay summarizes my 40 years of research in immunology. As a young physician, I encountered a patient with Waldenström's macroglobulinemia, and this inspired me to study the structure of IgM. I began to ask how antibody responses are regulated. In the late 1960s, the essential role of T cells in antibody production had been reported. In search of molecules mediating T cell helper function, I discovered activities in the culture supernatant of T cells that induced proliferation and differentiation of B cells. This led to my life's work: studying one of those factors, interleukin-6 (IL-6). To my surprise, IL-6 turned out to play additional roles, including myeloma growth factor and hepatocyte-stimulating factor activities. More importantly, it was involved in a number of diseases, such as rheumatoid arthritis and Castleman's disease. I feel exceptionally fortunate that my work not only revealed the framework of cytokine signaling, including identification of the IL-6 receptor, gp130, NF-IL6, STAT3, and SOCS-1, but also led to the development of a new therapy for chronic inflammatory diseases.

Personal Name as Subject:
Kishimoto T

PMID: 15771564 [PubMed - indexed for MEDLINE]

Scheinberg MA, Chapira E, Fernandes ML, Hubscher O.


[PubMed - indexed for MEDLINE]
Tocilizumab é um anticorpo humanizado contra o receptor de IL-6 introduzido na prática clínica na terceira semana de Maio deste ano para uso em pacientes com Artrite Reumatóide. O Hospital Israelita Albert Einstein e o Hospital Abreu Sodré- AACD são centros que atuam em pesquisa básica e clínica no desenvolvimento do produto.
Biológicos em Uso Anteriormente

- Anti TNFs 21
- Rituximabe 3
- Abatacept 3
- Primeira Linha 4
Anti-interleukin 6: first line in rheumatoid arthritis?

Marti L, Scheinberg M.

Clinical Rheumatology

Journal of the International League of Associations for Rheumatology

Anti-interleukin 6: first line in rheumatoid arthritis?

Luciana Marty & Morton Scheinberg

DOI 10.1007/s10067-009-1182-3

The use of ustekinumab in autoimmune disease.
Ryan C, Thrash B, Warren RB, Menter A.
Significant efficacy in the treatment of chronic plaque psoriasis
Promising results in Phase 2 studies in psoriatic arthritis
Could anti IL12/23 therapy replace anti-TNF biologics?
Why do some biologic agents induce psoriasis or psoriasiform lesions?
Laurindo IM, Scheinberg M.
Nat Clin Pract Rheumatol. 2008 Apr
Early steps of the inflammatory cascade lead to activation of T cells

Recently described phenotype Th17, a new subset of T cells

Expression of IL12 and IL23 with a common p40 subunit

Fully human monoclonal antibody anti IL12/23
IL-17 in synovial fluids from patients with rheumatoid arthritis ...

Levels of IL-17 in synovial fluids were significantly higher in rheumatoid arthritis (RA) patients than osteoarthritis (OA) patients. Anti-IL-17 antibody ...
New targets? Which targets are we talking about?
- Anti cytokines
- **Anti B cell therapy**
- Inhibitors of T cell co stimulation
- Anti cell adhesion molecules
- Inhibitors of intracelullar signalling
- Others
Role of B cells in autoimmunity

IL-10, interferon
Costimulatory ligand receptor
MHC/antigen-TCR
B cell
T cell
Autoantibodies
Organ damage

Antigen presenting (dendritic) cell

TACI
BLyS, APRIL

Papel das Células B

Apresentação de Antígenos
Rituximab na AR

Edwards e Cambridge 2001

- Cinco pacientes
- Sexo feminino, 55 anos
- Duração media da doença 22 anos
- Falha a cinco DMARDs
- Doença ativa
- Fator reumatóide
As células B como alvo no tratamento da AR
Efficacy of B-Cell–Targeted Therapy with Rituximab in Patients with Rheumatoid Arthritis

Jonathan C.W. Edwards, M.D., Leszek Szczępanski, M.D., Ph.D., Jacek Szeciński, M.D., Ph.D., Anna Filipowicz-Sosnowska, M.D., Ph.D., Paul Emery, M.D., David R. Close, Ph.D., Randall M. Stevens, M.D., and Tim Shaw, B.Sc.
Rituximab in refractory autoimmune diseases: Brazilian experience with 29 patients (2002-2004).

Scheinberg M, Hamerschlak N, Kutner JM, Ribeiro AA, Ferreira E, Goldenberg J, Kiss MH, Chahade WH.

[PubMed - indexed for MEDLINE]
Anti-cyclic citrullinated peptide antibodies in advanced rheumatoid arthritis.

Pinheiro GC, Scheinberg MA, Aparecida da Silva M, Maciel S.

New approaches of B-cell-directed therapy: beyond rituximab.
Dörner T, Burmester GR.
B-Lymphocyte Stimulator (BLyS)

- Member of TNF ligand super family
  - Expressed as 285 amino acid transmembrane protein, cleaved to 152 amino acid trimeric soluble protein
- Binds 3 receptors, TACI, BCMA, or BAFF-R expressed on B cells
- Promotes B-cell differentiation, Ig class switching, and survival
- Serum levels of BLyS correlate with disease activity in SLE patients

BLyS: Mechanism of Action

Antigens present in the periphery

Monocytes, activated by antigen, express membrane bound BLyS

BLyS is cleaved to active, soluble form

B cell survival, differentiation, & antibody formation

Soluble BLyS binds to activated B cells

Activated B cell
Belimumab Inhibits BLyS

Autoimmune Disease

Belimumab Binds Soluble BLyS

BLyS

TACI, BCMA, or BAFF-R

B-cell survival

B-cell apoptosis

Belimumab

BLISS Phase 3 Clinical Trial Program

1,693 patients from 223 centers in 31 countries
BLISS-52 Study Objectives

- To evaluate the efficacy of belimumab in subjects with SLE
- To evaluate the safety and tolerability of belimumab in subjects with SLE
- To evaluate the impact of belimumab on quality of life in subjects with SLE
Atacicept, a novel B cell-targeting biological therapy for the treatment of rheumatoid arthritis.

Bracewell C, Isaacs JD, Emery P, Ng WF.

Newcastle University, Musculoskeletal Research Group and Wilson Horne Immunotherapy Centre, Institute of Cellular Medicine, Newcastle-upon-Tyne, UK
“Um estudo randomizado, duplo-cego, placebo controlado, multicêntrico, prospectivo de procura de dose, Fase II/III com atacicept administrado subcutaneamente em sujeitos que experimentaram recentemente um Flare de lupús eritematoso sistêmico (LES).”
“Estudo randomizado, duplo-cego, controlado por placebo, multicêntrico, de Fase II para determinação da dose de atacicept administrado de forma subcutânea em indivíduos com artrite reumatóide e resposta inadequada a terapia com antagonista TNFá.”
Targeting CD22 as a strategy for treating systemic autoimmune diseases.
Dörner T, Goldenberg
MODULATION RATHER THAN DEPLETION OF B CELLS
Ocrelizumab: a step forward in the evolution of B-cell therapy.
Discontinuation of the Ocrelizumab programme in the RA indication

- Decision to discontinue the RA development programme was based on the ocrelizumab benefit/risk profile not demonstrating additional value in comparison to rituximab, in a TNF-IR population.

- The phase II clinical development programme in Relapsing Remitting Multiple Sclerosis (RRMS) is ongoing.
Rituximab: Growing Long Term Safety Experience

Clinical Trial Experience
- More than 9,000 patient years of exposure in a clinical trial setting
- More than 1,000 patients received > 5 courses
- 587 patients with > 5 Years exposure

Worldwide Post-Marketing setting
- More than 118,000 RA patients treated with rituximab since its launch in 2006
### Ocrelizumab and Rituximab Molecular Differences

<table>
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<tr>
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<th>Rituximab</th>
<th>Ocrelizumab</th>
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<tbody>
<tr>
<td>Antibody type</td>
<td>Chimeric</td>
<td>Humanized</td>
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<tr>
<td>Homology</td>
<td>11% overall sequence differences</td>
<td></td>
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<tr>
<td>Fc region</td>
<td>2 amino acid changes</td>
<td></td>
</tr>
<tr>
<td>Affinity to CD20</td>
<td>Similar</td>
<td></td>
</tr>
<tr>
<td>Epitope on CD20</td>
<td>Different but overlapping region of ECD</td>
<td></td>
</tr>
<tr>
<td>ADCC activity in vitro</td>
<td>-</td>
<td>* Enhanced ADCC potency (3-5 folds)</td>
</tr>
<tr>
<td>CDC activity in vitro</td>
<td>-</td>
<td>* Reduced CDC potency (2-3 folds)</td>
</tr>
</tbody>
</table>

The exact clinical significance of these molecular differences with respect to safety and efficacy is under further evaluation

*Ocrelizumab [data on file]. South San Francisco (CA): Genentech; 2003
New targets? Which targets are we talking about?

- Anti cytokines
- Anti B cell therapy
- Inhibitors of intracellular signalling
- Inhibitors of T cell co stimulation
- Anti cell adhesion molecules
- Others
Curr Opin Rheumatol. 2010 Feb 16. [Epub ahead of print]
Cohen S, Fleischmann R.
Metroplex Clinical Research Center, Dallas, Texas, Internal Medicine, UT Southwestern Medical School, Dallas, Texas, USA.
- P38 mitogen activated kinases
- Janus family of kinases
- Spleen tyrosine kinase (SyK)
New targets? Which targets are we talking about?

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- Inhibitors of intracellular signalling
- **Inhibitors of T cell co stimulation**
- Anti cell adhesion molecules
- Others
Curr Opin Rheumatol. 2009 May;21(3):244-50.

Costimulation blockade in rheumatic diseases: where we are

Costimulatory blockade with belatacept in clinical and experimental transplantation - a review.
Emamaullee J, Toso C, Merani S, Shapiro AM.
New targets? Which targets are we talking about?

- Anti cytokines
- Anti B cell therapy
- Inhibitors of intracellular signalling
- Inhibitors of T cell co stimulation
- **Anti cell adhesion molecules**
- Others
Cell adhesion molecules and inflammatory arthritis

Trials in inflammatory arthritis giving modest results-case of efalizumab

Natalizumab licensed for MS and Crohn's
New targets? Which targets are we talking about?

- Anti cytokines
- Anti B cell therapy
- Inhibitors of intracellular signalling

- Inhibitors of T cell co-stimulation
- Anti cell adhesion molecules
- Others
Do we need more TNF blockers?
Efficacy Sustained After Dose De-escalation of Certolizumab Pegol in Rheumatoid Arthritis Patients: Post-hoc Analysis of the RAPID 2 Open-label Extension

JS Smolen,¹ RF van Vollenhoven,² A Kavanaugh,³ K Luijtens,⁴ N Goel,⁵ D van der Heijde,⁶ JR Curtis⁷

¹Division of Rheumatology, Medical University of Vienna and Hietzing Hospital, Vienna, Austria; ²Department of Rheumatology, Karolinska Institute, Stockholm, Sweden; ³Division of Rheumatology, Allergy and Immunology, UCSD, La Jolla, CA, USA; ⁴Biostatistics, UCB, Brussels, Belgium; ⁵UCB, Smyrna, GA, USA; ⁶Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands; ⁷Division of Clinical Rheumatology and Immunology, University of Alabama at Birmingham, Birmingham, AL, USA
Biosimilar?

The world's first bio-similar antibody from India.
Protein Microheterogeneity

Small Molecule Drug

Protein Drug
Biotech products

Biotech products are very complex, sensitive, heterogenous mixtures of protein molecules.

- Each molecular entity of that mixture is characterized by specific physical, chemical and biological properties.

- Any change in the composition of that mixture is potentially going to affect patients safety and chance of cure.
Biosimilarity in primary structure and molecular conformation.

Edman sequencing of the amino acid sequence of the N-terminus of the heavy chain and of the light chain of REDITUX™ is similar with RMP.

**Molecular Conformation**

**Light Chain**

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<th>2</th>
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**Heavy Chain**

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Secondary and Tertiary structural conformation using Far UV CD Spectroscopy and Fluorescence Spectroscopy show comparability between REDITUX™ and RMP.
Biosimilar ?
Conclusions:

Exciting times are ahead for the patients with rheumatoid arthritis and for the doctors taking care of the respective patients. Lessons from the last decade with TNF blockers and the introduction of new biologics like abatacept, anti IL-6 new anti cytokines and the possibility of biologic oral medication should make the next decade full of excitement on the transition from bench to bedside. We should expect a more precise multidisciplinary approach outline on the next slide and the possibility to tailor the therapy coupled with specific biomarkers shown on the last slide.
The Future: Pharmacogenetics and “Personalized” Medicine

- Benefit + Toxicity
- No benefit + Toxicity
- No benefit No toxicity
- + Benefit No toxicity

All patients with the same diagnosis

Biotech Pharmaceuticals – Where do we stand today?

- Biotechnology has produced medical treatment for hitherto serious incurable diseases. About 250 biotech drugs approved for 380 indications.
- More than 300 biotech products are in clinical trials targeting more than 200 diseases, including cancer treatment (40%), auto-immune diseases etc.
- Biotech drugs accounting 20% of the world pharma market.
- 50% of new drugs are biodrugs.

Source: IMS 2008
Thank you very much. Hope that all will have a safe journey back to their respective countries including myself.