# LE CRITICITÀ DELLA TERAPIA BIOLOGICA

29 Novembre 2008
Hilton Garden Inn - Firenze

## Biologici di II^ generazione (Rituximab e Abatacept) : safety

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# New therapies for treatment of rheumatoid arthritis

Josef S Smolen, Daniel Aletaha, Marcus Koeller, Michael H Weisman, Paul Emery

Rheumatoid arthritis is characterised by pain, swelling, and destruction of joints, with resultant disability. Only disease-modifying antirheumatic drugs can interfere with the disease process. In the past few years, biological agents, especially inhibitors of tumour necrosis factor, have allowed for hitherto unseen therapeutic benefit, although even with these drugs the frequency and degree of responses are restricted. Therefore, new agents are needed, and three novel biological compounds for treatment of rheumatoid arthritis have already been used in practice or are on the horizon: rituximab (anti-CD20), abatacept (cytotoxic T-lymphocyte antigen 4 immunoglobulin), and tocilizumab (anti-interleukin 6 receptor). We discuss the targets of these drugs, the roles of these targets in the pathogenesis of rheumatoid arthritis, and the efficacy and adverse effects of these agents from clinical trial data. Novel therapeutic strategies in conjunction with optimised disease assessment for better treatment of rheumatoid arthritis and an outlook into potential future targets are also presented.

# Reasons for discontinuation within the first year of treatment

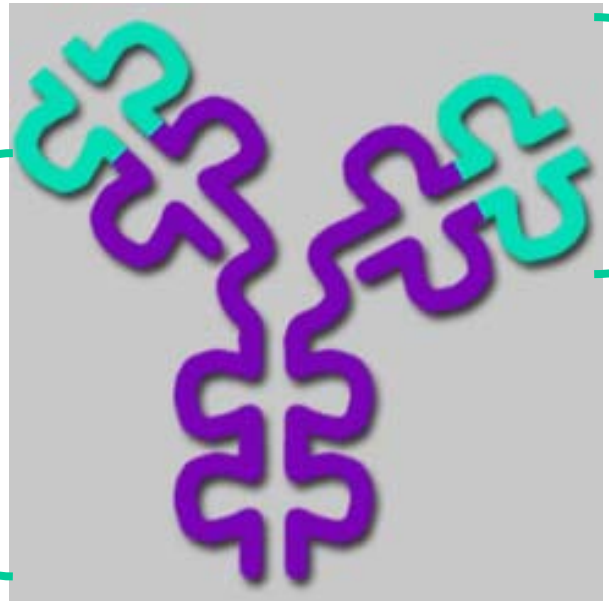
| | Adalimumab (n=94) No(%) | Infliximab (n=83) No(%) | Etanercept (n=14) No(%) | Total (n=191) No(%) |
|---|---|---|---|---|
| Inefficacy | 10 (11) | 8 (10) | 1 (7) | 10 (11) |
| Adverse events | 10 (11) | 20 (24) | 1 (7) | 31 (16) |
| Combination | 1 (1) | 5 (6) | 0 (0) | 6 (3) |
| Other* | 3 (3) | 2 (2) | 2 (14) | 7 (4) |
| Total | 24 (26) | 35 (42) | 4 (29) | 63 (33) |

* Pregnancy and patient initiative

Flendrie M et al, Ann.Rheum Dis 2003, 62S:30-3

# *"Si sentiva l'esigenza di un nuovo biologico?"*

## The structure of rituximab



Rituximab comprises human IgG and $\kappa$-constant regions

The variable region is from the anti-CD20 murine antibody fragment IDEC-2B8

ybak et al. Proc Natl Acad Sci USA 1992;89:3165–3169; Shaw et al. Ann Rheum Dis 2003; 62(Suppl :55–59; Silverman et al. Arthritis Rheum 2003;48:1484–1492

# *"1° motivo"*

B cells play an important role in the pathogenesis of RA

They secrete autoantibodies

They are efficient APCs

They secrete cytokines, potentiating chronic inflammation

They play an important role in synovial structure and organisation

CD20 provides an excellent B cell surface target for immunomodulatory therapy

Rituximab potently depletes B cells by targeting CD20

**ohn Isaacs MB BS, PhD, FRCP**

**rofessor of Clinical Rheumatology, Director, Wilson Horne Immunotherapy Centre, University of**

# *"2° motivo"*

- La risposta agli anti TNF-α è nella pratica clinica buona, ma la remissione della malattia riguarda una quota parte di pazienti;
- Occorre l'ausilio, spesso determinante, del methotrexate;
- Recidive intervengono alla sospensione degli anti TNF-α, anche quando il risultato terapeutico è stato buono.

**letaha D, Smolen JS. The definition and measurement of disease modification in inflammatory heumatic diseases. Rheum Dis Clin North Am 2006;32:9–44.**

# *“3° motivo”*

- Gli anti TNF-α sono gravati da effetti collaterali ed il loro monitoraggio richiede un particolare impegno assistenziale (pratica clinica).

# *“4° motivo”*

- Ci sono precise controindicazioni all’impiego degli anti TNF-α, che restringono il numero di soggetti che possono adire ad un programma di terapia con gli anti TNF-α (storia pregressa di tubercolosi; malattia demielinizzante; pregressa neoplasia; cardiopatia severa; etc..).

# *“5° motivo”*

- I costi dei biologici (benché compensati da una riduzione dei costi indiretti dell’AR) restano elevati e ciò ne limita un impiego più estensivo.

# Rituximab

OPEN QUESTIONS:

How long to use rituximab?

# *"Effetti collaterali"*

- L'estrapolazione degli effetti collaterali osservati nei pazienti con Linfoma non Hodgkin riferendola ai pazienti con AR non è corretta, così come sono diversi i farmaci concomitanti e le patologie associate.

# *"Eventi avversi"*

## Comunicazione AIFA: **Aprile 2007**

- 2 casi di leucoencefalopatia multifocale progressiva (PML) ad esito fatale in soggetti affetti da LES e trattati con Rituximab;
- 1 caso ad esito fatale in corso di vasculite.
- 1 caso identificato in AR ARD 2008;67:SupplIII

Tali patologie (il Rituximab era utilizzato fuori indicazione) sono state causate dall'attivazione del virus SL, un poliomavirus presente nell'80% della popolazione e che si può attivare in corso di trattamenti immunosoppressivi.

REVIEW

# Consensus statement on the use of rituximab in patients with rheumatoid arthritis

J S Smolen, E C Keystone, P Emery, F C Breedveld, N Betteridge, G R Burmester, M Dougados, G Ferraccioli, U Jaeger, L Klareskog, T K Kvien, E Martin-Mola, K Pavelka, The Working Group on the Rituximab Consensus Statement

*Ann Rheum Dis* 2007;**66**:143–150. doi: 10.1136/ard.2006.061002

**Indication**

•Rheumatoid arthritis (RA) with inadequate response to (or intolerance of) tumour necrosis factor (TNF) inhibitors

– Active RA (at least moderate disease activity)

• Possibly: RA with contraindication to TNF inhibitors (especially lymphoma) and inadequate response to disease-modifying antirheumatic drugs such as methotrexate (MTX)

# *"Indicazioni delle autorità regolatorie"*

## FDA ed EMEA

- Il Rituximab può essere usato in pazienti con AR i quali possono essere trattati con agenti biologici ed hanno avuto una risposta inadeguata o un'intolleranza ad 1 o più anti TNF-α;
- (Pazienti con controindicazioni agli anti TNF-α non sono ancora stati studiati).


ohen S, Emery P, Greenwald M, Dougados M, Furie R, Genovese M, et al. Rituximab for rheumatoid arthritis fractory to anti-tumor necrosis factor therapy. Arthritis Rheum 2006;54:2739–806.

mery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, et al. The efficacy d safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phas b doubleblind, placebo-controlled, dose-ranging trial (DANCER). Arthritis Rheum 2006;54:1390–400.

tuximab. Full prescribing information. 2006.

# *"Criteri di esclusione per Rituximab"*

- Scompenso cardiaco di grado severo IV classe NYHA **(per gli anti TNF-α di classe II e III).**

- Ipersensibilità al Rituximab o alle proteine muriniche.

- Gravidanza.

**ituximab. Full prescribing information. 2006.**
**ttp://www.gene.com/gene/products/information/oncology/rituxan/insert.jsp (accessed 4 Nov 2006).**

# *"Criteri di esclusione per Rituximab"*

- Pazienti con evidenza di impegno sistemico importante, con altre severe patologie ed anomalie laboratoristiche ed una **storia di infezioni recidivanti importanti**.


ohen S, Emery P, Greenwald M, Dougados M, Furie R, Genovese M, et al. Rituximab for heumatoid arthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum 006;54:2739–806.

mery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, avanaugh A, et al. The efficacy and safety of rituximab in patients with active heumatoid arthritis despite methotrexate treatment: results of a phase IIb doubleblind, lacebo-controlled, dose-ranging trial (DANCER). Arthritis Rheum 2006;54:1390–400.


# *"TBC"*

- Non ci sono evidenze di un'aumentata frequenza di TBC nei pazienti con linfoma trattato con rituximab ed inoltre, attualmente, non c'è evidenza che indichi la necessità di uno screening sistematico per i pazienti con AR che debbano essere trattati con Rituximab.

imby E. Tolerability and safety of rituximab (MabThera). Cancer Treat Rev 2005;31:456–73.

# *"Rx torace"*

- Una radiografia del torace è stata utilizzata nei vari trials clinici, non è ritenuta obbligatoria (ma è consigliabile).

Rheumatology 2008 47(5):738-739

# Rituximab in rheumatoid arthritis following anti-TNF-associated tuberculosis

**M. L. Burr, A. P. Malaviya, J. H. Gaston, A. J. Carmichael** and **A. J. K. Östör**

SIR,

The link between anti-TNF therapy and reactivation of latent tuberculosis (TB) is well recognized [1–3]. These patients are more likely to present with disseminated infection and this carries considerable mortality. Managing active RA in patients with anti-TNF-associated TB can therefore be challenging. We present the case of a patient with RA who was successfully treated with rituximab, a chimaeric anti-CD20 monoclonal antibody, after developing disseminated isoniazid-resistant TB following treatment with infliximab.

A 54-yr-old white female with a 15-yr history of severe .

# *"Screening per epatite B e C"*

- E' facoltativo (sebbene opportuno), ma il parere degli esperti è che la condizione di malattia da epatite B debba essere nota.

eo W, Johnson PJ. Diagnosis, prevention and management of hepatitis B virus reactivation during nticancer therapy. Hepatology 2006;43:209–20.

# *"Profilassi nell'epatite B"*

## Dalla letteratura oncologica:

- I pazienti con epatite C sono stati trattati senza ulteriore profilassi (A);
- Quelli con epatite B sono stati trattati di solito con lamivudina (B-C);
- Tuttavia sono stati riportati casi di epatite fulminante e di zoster fulminante (D);
- Non ci sono evidenze per l'AR positiva al virus HBV (E-F).


Ramose-Casals M, et al..; SS-HCV Study Group. Treatment of B-cell lymphoma with rituximab in two patients with Sjogren's ndrome associated with hepatitis C virus infection. Lupus 2004;13:969–71.

Yeo W, Johnson PJ. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. Hepatology 06; 43:209–20.

Skrabs C, et al.. Treatment of HBV-carrying lymphoma patients with rituximab and CHOP: a diagnostic and therapeutic challenge. ukemia 2002;16:1884–6.

Hamaki T, et al. Prophylaxis of hepatitis B reactivation using lamivudine in a patient receiving rituximab. Am J Hematol 2001; :292–4.

Kimby E. Tolerability and safety of rituximab (MabThera). Cancer Treat Rev 2005;31:456–73.

Emery P. Treatment of rheumatoid arthritis. BMJ 2006;332:152–5.

## *"Quale intervallo di tempo deve trascorrere tra l'utilizzo del Rituximab ed un anti TNF-α o viceversa?"*

- Etanercept = 4 settimane
- Infliximab = 8 settimane
- Adalimumab = 8 settimane
- Non ci sono evidenze di un aumento significativo del rischio di infezioni o di altri eventi avversi in pazienti che hanno iniziato il rituximab dopo un anti TNF-α in confronto a pazienti che hanno utilizzato il rituximab dopo un trattamento con farmaci tradizionali.

**reedveld FC, Kim D, Agarwal S, Cooper S, Burke L, Matteson EL, et al. Safety of TNF inhibitors in heumatoid arthritis patients previously treated with rituximab [abstract]. Ann Rheum Dis 006;65(Suppl 1):THU0206.**

# *"Si può ritrattare il paziente?"*

- Mediamente dopo 6 o più mesi; un intervallo ottimale di ritrattamento è in corso di studio.


**an Vollenhoven RF, Cohen S, Pavelka K, Kavanaugh A, Tak PP, Greenwald M, et al. Response to tuximab in patients with rheumatoid arthritis is maintained by repeat therapy: results of an open-bel trial [abstract]. Ann Rheum Dis 2006;65:SAT0197.**

**eystone E, Fleischmann R, Emery P, Chubick A, Dougados M, Baldassare AR, et al. Long-term fficacy and safety of a repeat treatment course of rituximab in rheumatoid arthritis in patients with n inadequate response to one or more TNF inhibitors [abstract]. Ann Rheum Dis 2006;65(Suppl**

Rheumatology 2007;46:626–630
Advance Access publication 19 December 2006
doi:10.1093/rheumatology/kel393

# Repeated B lymphocyte depletion with rituximab in rheumatoid arthritis over 7 yrs

C. Popa, M. J. Leandro, G. Cambridge and J. C. W. Edwards

- To assess safety and efficacy of repeated B-cell depletion with rituximab in patients with rheumatoid arthritis

- Thirty-seven patients with refractory RA entered into a programme of repeated B-lymphocyte depletion (up to 5 cycles, 89 cycles in total) with protocols based on the anti-CD20 monoclonal antibody, rituximab, have been observed over periods of >5 yrs (n=22) or 3–5 yrs (n=14).

Rheumatology 2007;46:626–630
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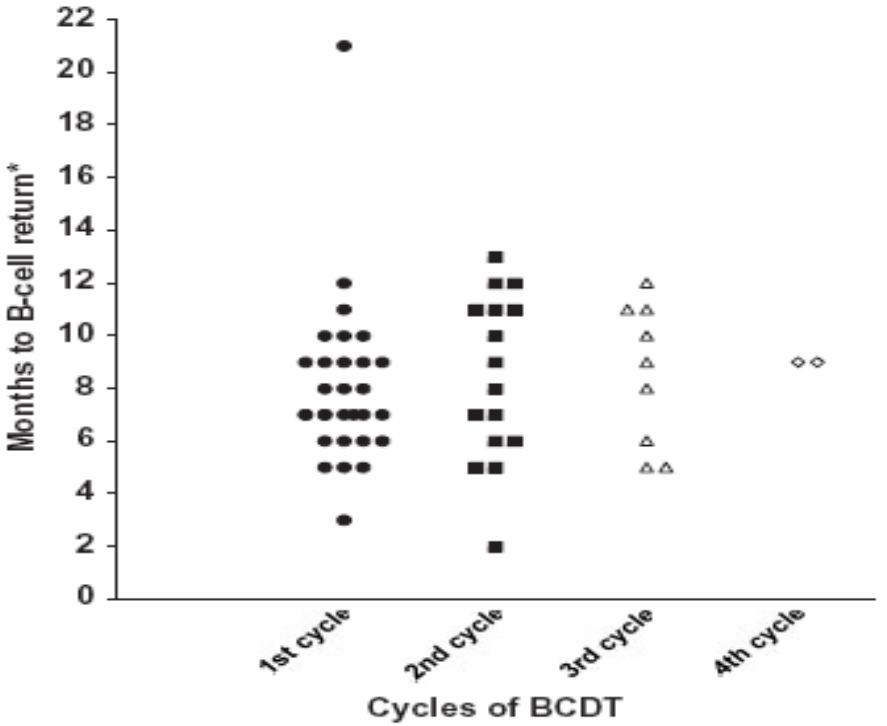
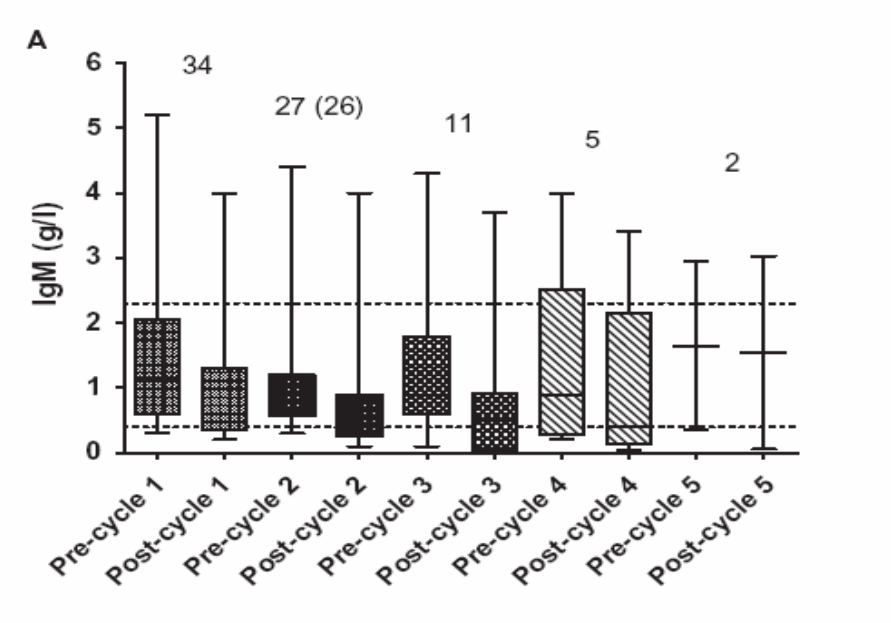
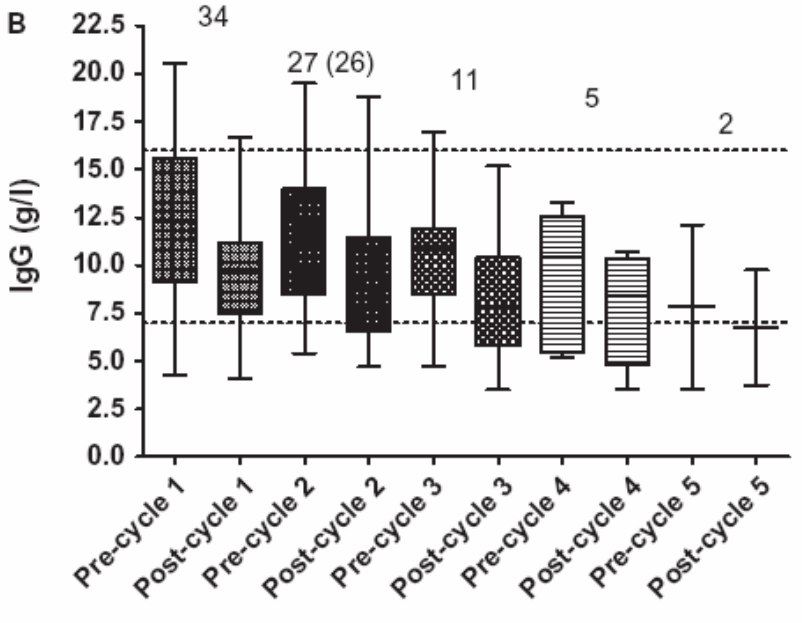
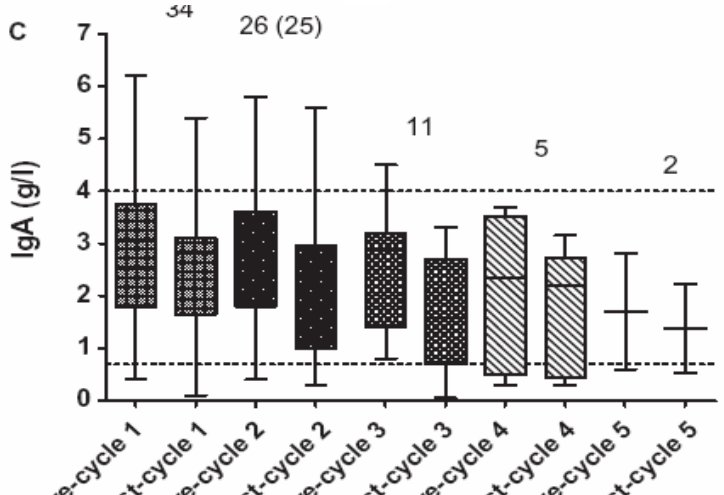



FIG. 3. Time in months to B-cell return to the periphery *(defined as CD19+ positive cells $>0.005 \times 10^9$/l) plotted for individual patients following successive cycles of B-cell depletion therapy (BCDT).

Changes in immunoglobulin levels associated with repeated cycles of B-lymphocyte depletion wi
rituximab.
(A) IgM (B) IgG (C) IgA.
Number of patients is given above each plot. Median, range, 25th and 75th percentile charted.




Susceptibility to respiratory infection (16 cases)

**Popa et al. Rheumatology 200**

Rheumatology 2007;46:626–630
Advance Access publication 19 December 2006
doi:10.1093/rheumatology/kel393

# Repeated B lymphocyte depletion with rituximab in rheumatoid arthritis over 7 yrs

C. Popa, M. J. Leandro, G. Cambridge and J. C. W. Edwards

## Summary


- Experience with repeated B-cell depletion therapy in RA suggests that 80% of seropositive patients may respond, and 50–60% become susceptible to continuing control of disease.

- Secondary resistance appears not to be a problem over 2–5 yrs.

- Susceptibility to respiratory infection may be increased and requires further surveillance.

- Cumulative effects on immunoglobulin levels may occur with frequently repeated usage and surveillance

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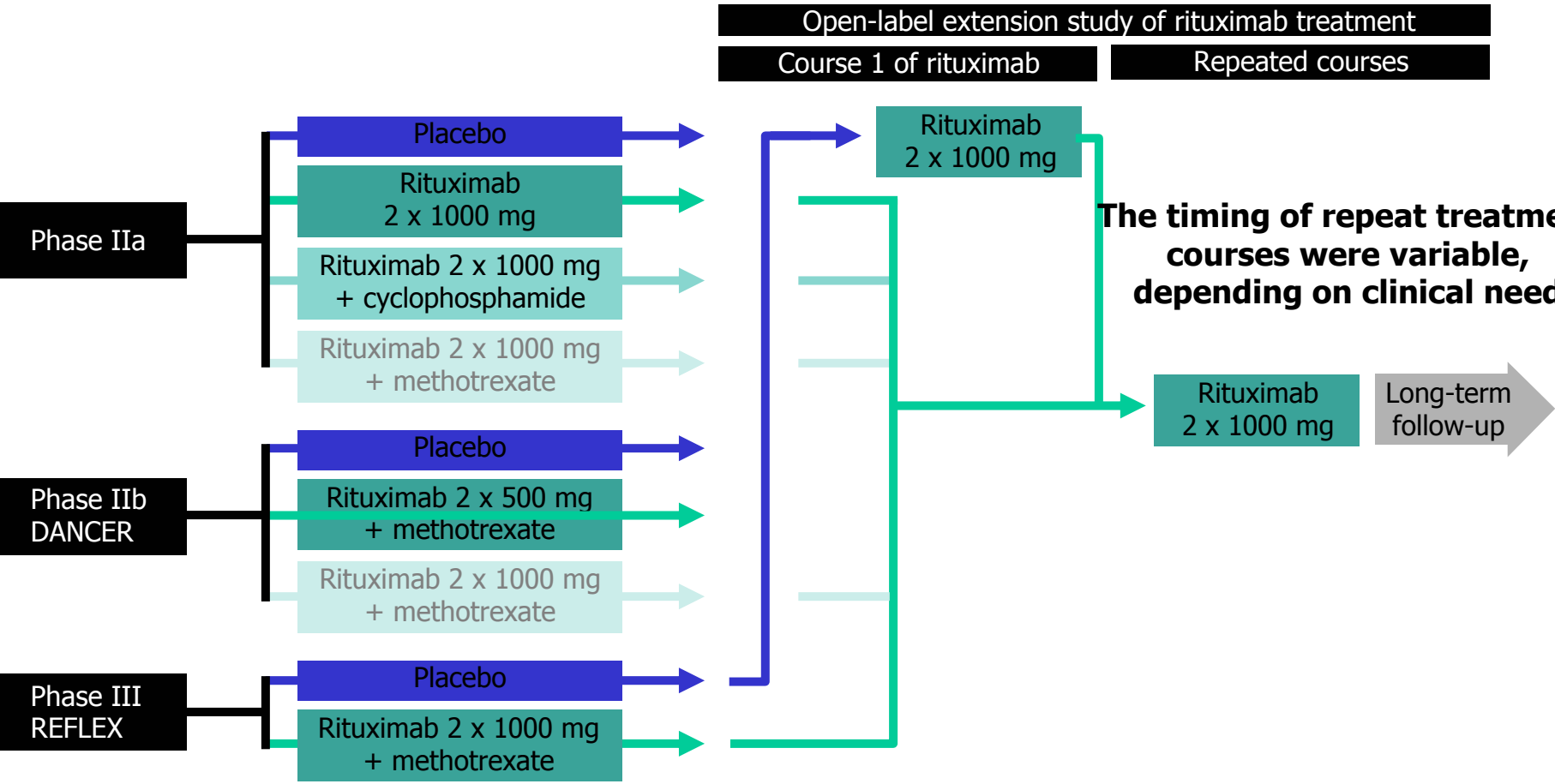
DOI 10.1002/art.23059


# Safety and Efficacy of Additional Courses of Rituximab in Patients With Active Rheumatoid Arthritis

## An Open-Label Extension Analysis

Edward Keystone,[1] Roy Fleischmann,[2] Paul Emery,[3] Daniel E. Furst,[4] Ronald van Vollenhoven,[5] Joan Bathon,[6] Maxime Dougados,[7] Andrew Baldassare,[8] Gianfranco Ferraccioli,[9] Andrew Chubick,[10] James Udell,[11] Matthew W. Cravets,[12] Sunil Agarwal,[13] Simon Cooper,[14] and Fabio Magrini[14]

# Protocol Design for Open-Label Extension Study of Rituximab in RA




All patients in the open-label extension study received weekly methotrexate (10–25 mg) and methylprednisolone 100 mg on Days 1 and 15 plus oral prednisone 60 mg/day on Days 2–7 and 30 mg/day on Days 8–14

# Keystone E, et al. A&R 2007

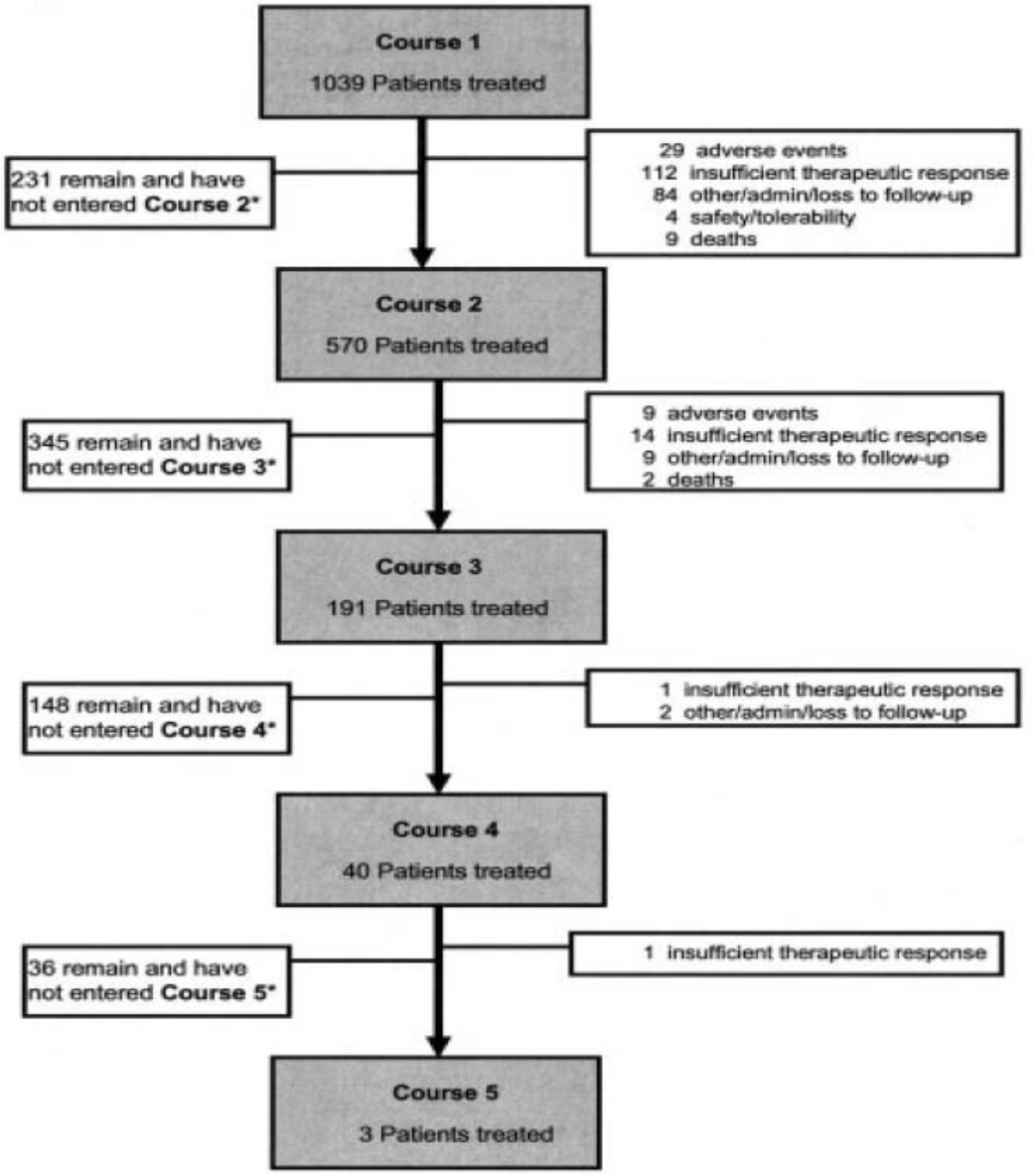
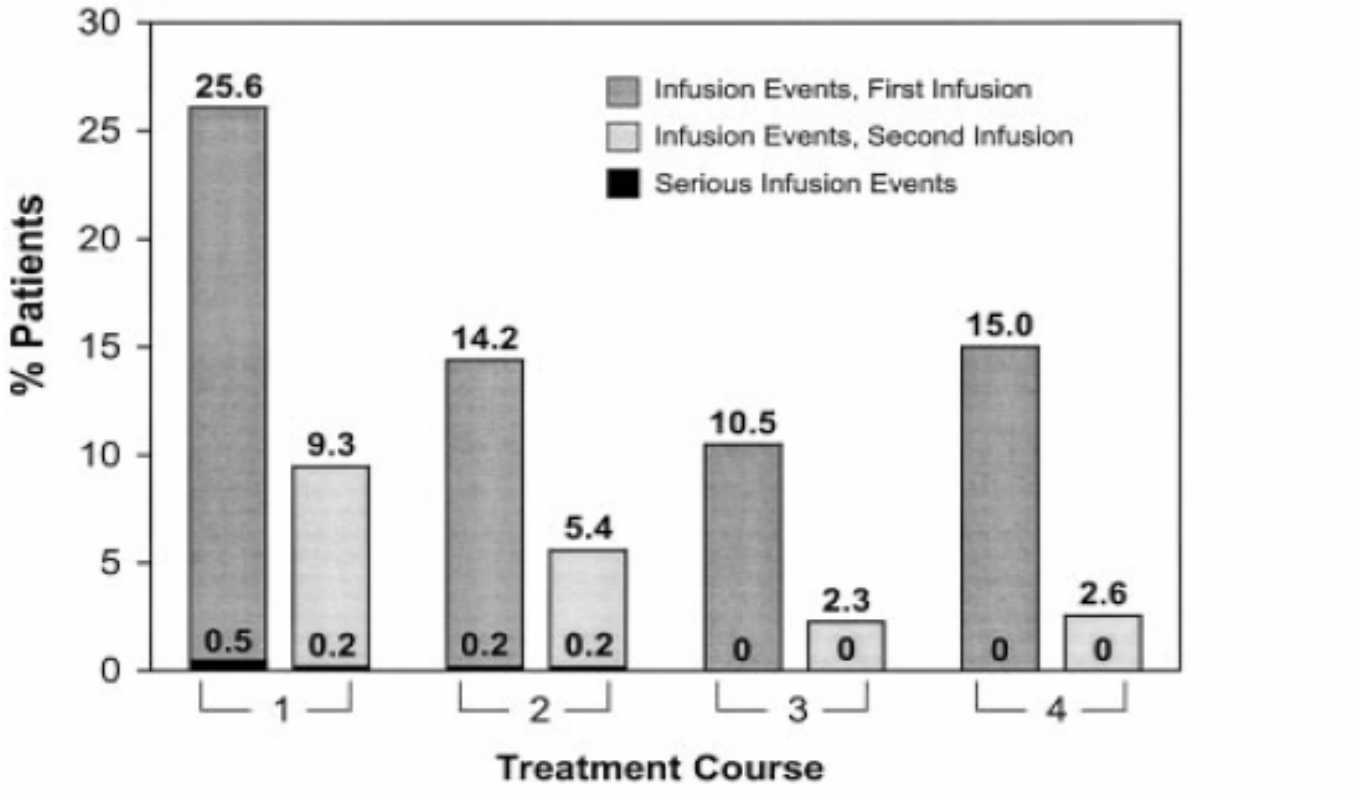


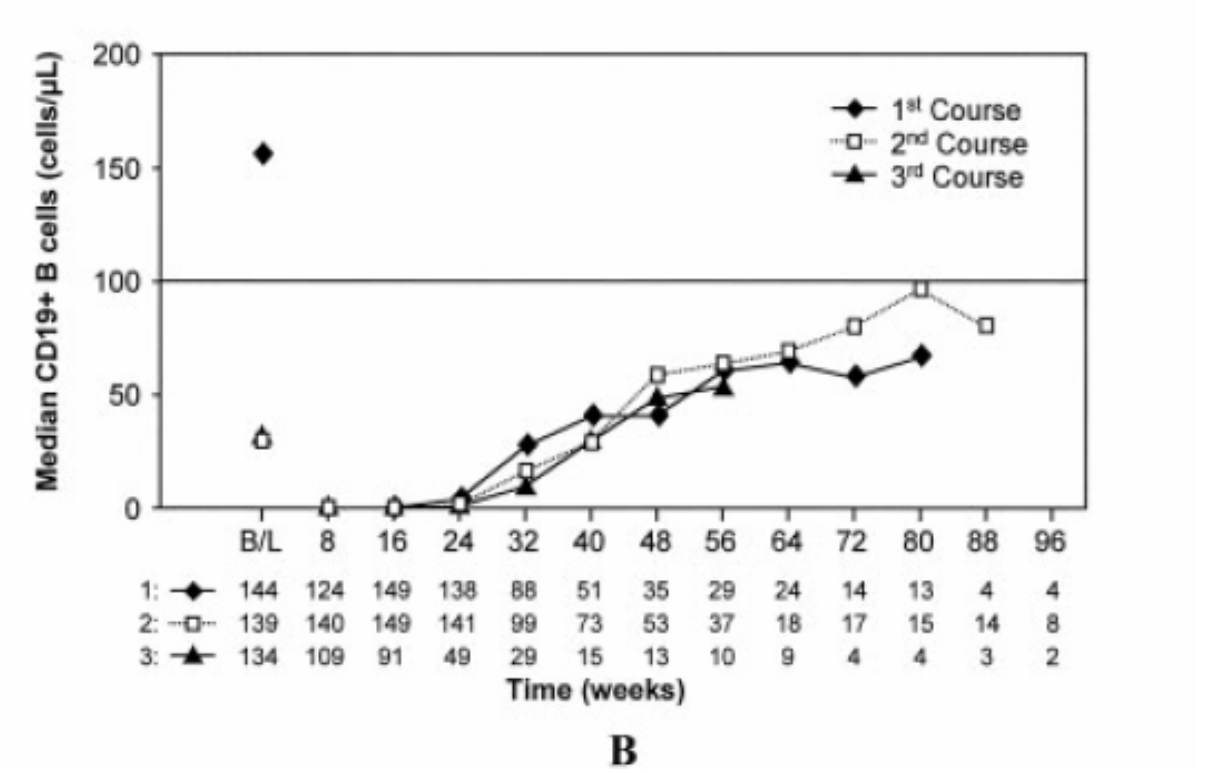

**Figure 1.** Flow chart of patient disposition. * = patients who did not receive the subsequent dose but continued to be included in the

## Keystone E, et al. A&R 2007




roportions of patients experiencing an acute infusion
eaction by treatment course. First infusions and second infusions are
resented for each course.

## Keystone E, et al. A&R 2007




CD19 cell counts in patients receiving up to
3 courses of rituximab (all-exposure population). Median CD19 cell counts, analyzed by flow cytometry, were reported from baseline (B/L)

# Keystone E, et al. A&R 2007

Table 3. Rate of serious infections in the all-exposure population compared with patients with IgM or IgG concentrations below the LLN and patients with IgM and IgG concentrations above the LLN at any time*

| | All-exposure population (n = 1,039) | Patients with IgM and IgG above LLN (n = 804) | Patients with IgM below LLN (n = 207) | Patients with IgG below LLN (n = 50) |
|---|---|---|---|---|
| No. (%) of patients with serious infections | 68 (6.5) | 45 (5.6) | 18 (8.7) | 6 (12.0) |
| Number of AEs/patient-years of exposure | 84/1,670.8 | 58/1,225.1 | 21/376.2 | 6/125.4 |
| Serious infection rates/100 patient-years | 5.0 | 4.7 | 5.6 | 4.8 |

* Multiple occurrences of the same event in a single patient were counted multiple times. Serious infections were defined as those reported as serious and/or treated with intravenous antibiotics. The lower limit of normal (LLN) was 5.2–6.7 mg/ml for IgG and 0.5 mg/ml for IgM, depending on the laboratory. AEs = adverse events.

# Safety of Biologic Therapy in Rheumatoid Arthritis and Other Autoimmune Diseases: Focus on Rituximab

Roy M. Fleischmann, MD

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**Seminars Arthritis Rheum 2008 in press**

Table 1 Adverse Events Reported in Phase II/III Randomized Clinical Trials of Rituximab in Rheumatoid Arthritis (38-40)

| | | Incidence (%) | | | | |
|---|---|---|---|---|---|---|
| Study | Treatment | All Adverse Events | Serious Adverse Events | Adverse Events Related to the First Infusion | All Infections | Serious Infections |
| Phase IIa | MTX ($n$ = 40) | 80 | 8 | 30 | NR | 2.5 |
| | RTX ($n$ = 40) | 80 | 5 | 45 | NR | 5 |
| | RTX + CycP ($n$ = 41) | 73 | 15 | 32 | NR | 5 |
| | RTX + MTX ($n$ = 40) | 85 | 8 | 33 | NR | 0 |
| Phase IIb | PBO ($n$ = 149) | 70 | 3 | 18 | 28 | 1 |
| | RTX 500 mg ($n$ = 124) | 81 | 7 | 31 | 35 | 0 |
| | RTX 1000 mg ($n$ = 192) | 85 | 7 | 38 | 35 | 2 |
| Phase III | MTX ($n$ = 209) | 88 | 10 | 23 | 38 | 1 |
| | RTX + MTX ($n$ = 308) | 85 | 7 | 29 | 41 | 2 |

CycP, cyclophosphamide; MTX, methotrexate; NR, not reported; PBO, placebo; RTX, rituximab.

# *"Monitoraggio degli effetti collaterali"*

- Reazioni infusionali nel 30-35%, talora severe (disponibilit
ella rianimazione e di farmaci quali paracetamolo
ntistaminici, broncodilatatori, glucocorticoidi, adrenalina
tc…); (1-2-3-4)

- Neutropenia (8%) fino ad un anno dal trattamento; (4)

- Anticorpi HACA (9,2%) antichimerici facilitano le reazion
llergiche. (3-4)


Cohen S, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum 2006;54:2739–806.
Emery P, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIb
ubleblind, placebo-controlled, dose-ranging trial (DANCER). Arthritis Rheum 2006;54:1390–400.
Edwards JC, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med 2004;350:2572–81.
Rituximab. Full prescribing information. 2006. http://www.gene.com/gene/ products/information/oncology/rituxan/insert.jsp (accessed 4 Nov 2006).

Table 2 Incidence of Adverse Events and Infections by Rituximab Treatment Course (52)

| Parameter | Course 1 ($n$ = 1053) | Course 2 ($n$ = 684) | Course 3 ($n$ = 400) | Course 4 ($n$ = 142) |
|---|---|---|---|---|
| AEs, $n$ (%) | 931 (88) | 553 (81) | 228 (72) | 93 (65) |
| Serious AEs, $n$ (%) | 187 (18) | 105 (15) | 39 (10) | 4 (3) |
| No. of infections | 1083 | 608 | 260 | 75 |
| Infections/100 patient-years (95% CI) | 79 (75; 84) | 85 (78; 92) | 97 (86; 110) | 101 (81; 127) |
| No. of serious infections | 73 | 33 | 17 | 4 |
| Serious infections/100 patient-years (95% CI) | 5.4 (4.3; 6.7) | 4.6 (3.3; 6.5) | 6.3 (3.9; 10.2) | 5.4 (2.0; 14.4) |

AE, adverse event; CI, confidence interval.

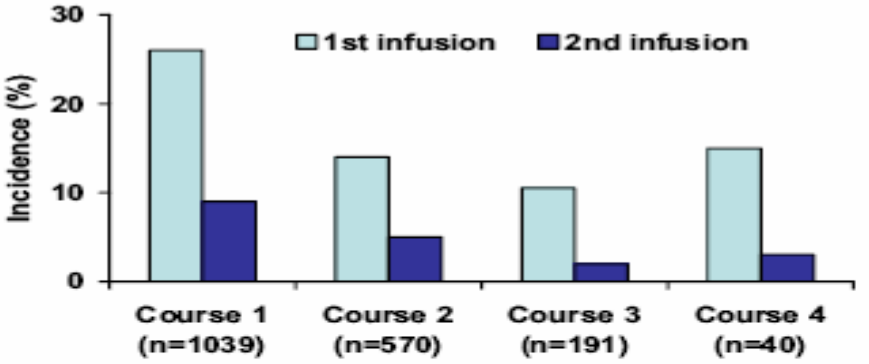


**Figure 1** Incidence of rituximab-related acute infusion reactions in patients with active RA (51). The proportion of patients experiencing an acute infusion reaction by treatment course in an open-label extension analysis of patients with active rheumatoid arthritis who had participated in 1 of the 3 double-blind rituximab clinical trials. Data for first infusions and second infusions are presented for each course. The numbers of patients receiving ≥1, ≥2, ≥3, and ≥4 courses of rituximab are shown in the $x$-axis labels.

# *"Serious Infections"*

- 4,7/100 - RTX vs 3,2/100 placebo pazienti anno (DANCER study)
- 5,2/100 - RTX vs 3,7/100 placebo pazienti anno (Reflex study)

**ohen S, Emery P, Greenwald M, Dougados M, Furie R, Genovese M, et al. Rituximab for rheumatoi rthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum 2006;54:2739–806.**
**Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, et a he efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate eatment: results of a phase IIb doubleblind, placebo-controlled, dose-ranging trial (DANCER). rthritis Rheum 2006;54:1390–400.**

Vol. 54, No. 9, September 2006, pp 2793–2806
DOI 10.1002/art.22025


# Rituximab for Rheumatoid Arthritis Refractory to Anti–Tumor Necrosis Factor Therapy

## Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Trial Evaluating Primary Efficacy and Safety at Twenty-Four Weeks

**Table 4.** Summary of adverse events (safety population)

| | No. (%) of patients taking placebo plus MTX (n = 209) | No. (%) of patients taking rituximab plus MTX (n = 308) |
|---|---|---|
| Adverse events | | |
| Any adverse event | 183 (88) | 261 (85) |
| Severe adverse event* | 49 (23) | 55 (18) |
| Related adverse event† | 77 (37) | 119 (39) |
| Serious adverse event | 21 (10) | 23 (7) |
| Adverse event leading to withdrawal | 2 (<1) | 8 (3) |
| Death | 0 | 0 |
| Adverse events reported at a ≥5% incidence | 183 (88) | 261 (85) |
| Rheumatoid arthritis | 87 (42) | 65 (21) |
| Headache | 19 (9) | 26 (8) |
| Upper respiratory tract infection | 14 (7) | 24 (8) |
| Nasopharyngitis | 12 (6) | 23 (7) |
| Nausea | 5 (2) | 22 (7) |
| Fatigue | 12 (6) | 21 (7) |
| Hypertension | 11 (5) | 21 (7) |
| Diarrhea | 16 (8) | 18 (6) |
| Arthralgia | 10 (5) | 17 (6) |
| Pyrexia | 7 (3) | 15 (5) |
| Dizziness | 8 (4) | 14 (5) |
| Bronchitis | 12 (6) | 13 (4) |
| Cough | 11 (5) | 10 (3) |
| Sinusitis | 11 (5) | 10 (3) |
| Urinary tract infection | 16 (8) | 10 (3) |

* Grade 3 or 4 according to the Cancer Therapy Evaluation Program Common Toxicity Criteria, version 2.0.
† Related to any study drug (rituximab, methotrexate [MTX], or glucocorticoids).

Vol. 54, No. 9, September 2006, pp 2793–2806
DOI 10.1002/art.22025


# Rituximab for Rheumatoid Arthritis Refractory to Anti–Tumor Necrosis Factor Therapy

## Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Trial Evaluating Primary Efficacy and Safety at Twenty-Four Weeks

**Table 5.** Acute infusion reactions from the first and second rituximab infusions*

| | No (%) of patients taking placebo plus MTX (n = 209) | | No (%) of patients taking rituximab plus MTX (n = 308) | |
|---|---|---|---|---|
| | First infusion | Second infusion | First infusion | Second infusion |
| Acute infusion reactions* | 38 (18) | 24 (11) | 72 (23) | 26 (8) |
| Headache | 10 (5) | 2 (<1) | 15 (5) | 3 (<1) |
| Hypertension | 4 (2) | 4 (2) | 9 (3) | 7 (2) |
| Nausea | 2 (<1) | – | 8 (3) | 2 (<1) |
| Pruritus | 2 (<1) | – | 7 (2) | – |
| Urticaria | 1 (<1) | – | 7 (2) | – |
| Diarrhea | 1 (<1) | 1 (<1) | 5 (2) | 3 (<1) |
| Flushing | 2 (<1) | 1 (<1) | 5 (2) | 2 (<1) |
| Pyrexia | 1 (<1) | 2 (<1) | 5 (2) | – |
| Dizziness | 4 (2) | 2 (<1) | 4 (1) | 2 (<1) |
| Hot flush | – | – | 4 (1) | 1 (<1) |
| Throat irritation | – | – | 4 (1) | 1 (<1) |
| Tachycardia | 7 (3) | – | 3 (<1) | 2 (<1) |
| Ear pruritus | – | – | 3 (<1) | – |
| Oropharyngeal swelling | – | – | 3 (<1) | – |
| Hypotension | – | 1 (<1) | 2 (<1) | 2 (<1) |
| Asthma | – | – | 2 (<1) | – |
| Vomiting | – | – | 1 (<1) | 2 (<1) |
| Rash | – | – | 1 (<1) | 1 (<1) |

* Values represent acute infusion reactions occurring in at least 2 rituximab-treated patients. MTX = methotrexate.

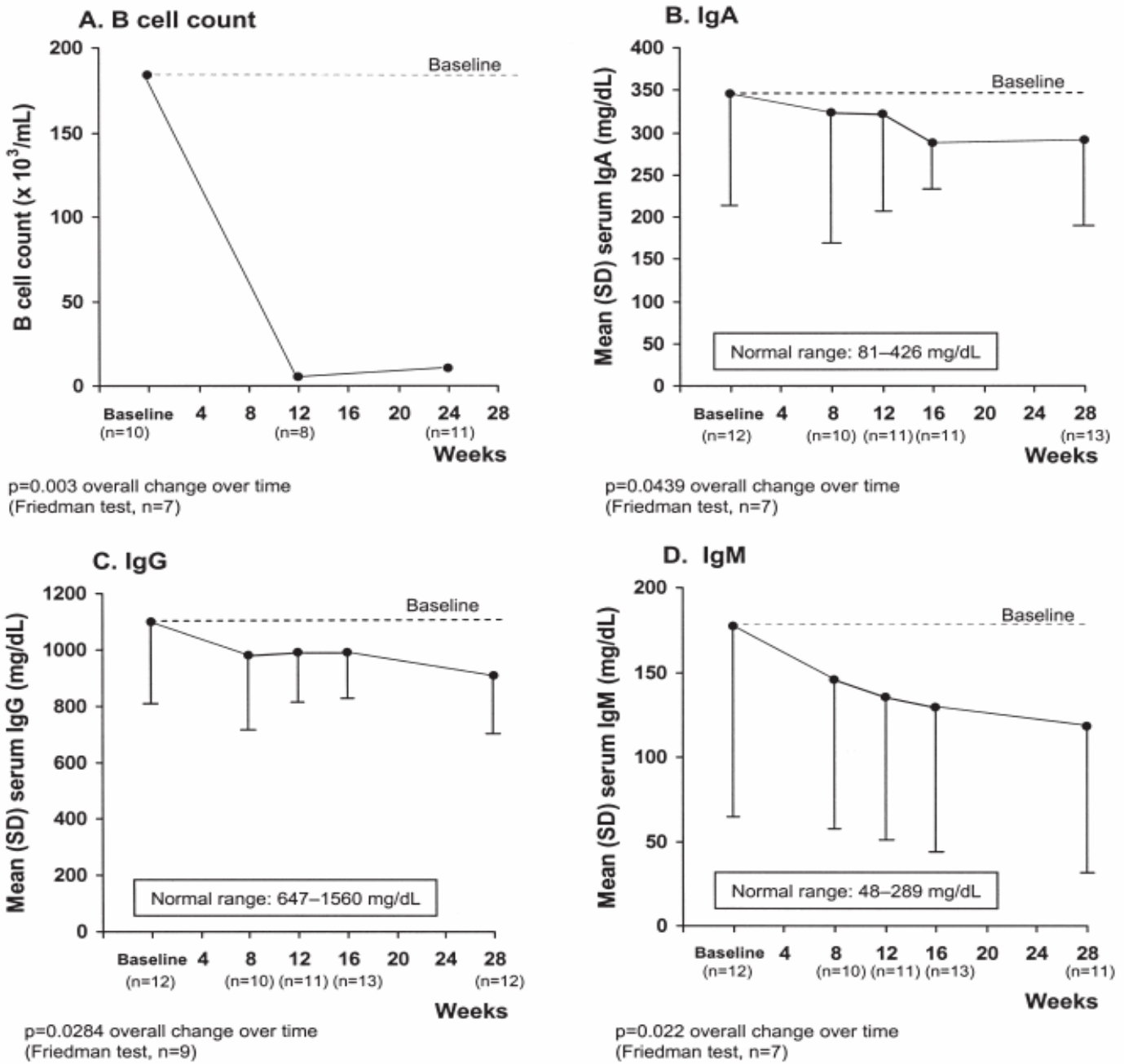


*Figure 6.* B cell depletion with minimal effect on immunoglobulin isotypes in patients with RA following treatment with rituximab.

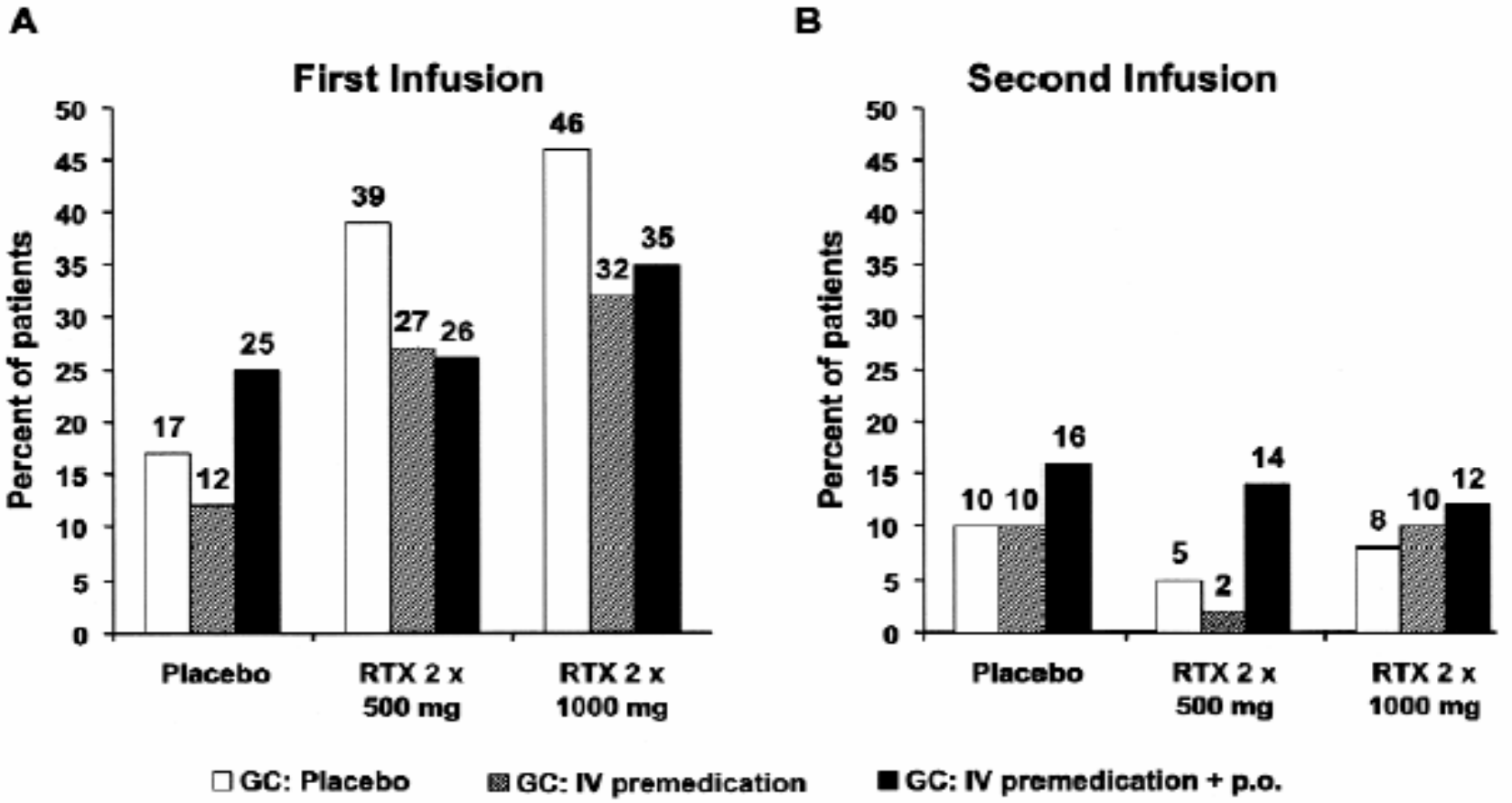


*Figure 3.* Infusion reactions from the rituximab Phase IIb DANCER Study[11]. A. Infusion reactions associated with the first infusion of RTX. B. Infusion reactions associated with the second infusion of RTX. GC: glucocorticoids; RTX: rituximab.

# FATTORI PREDITTIVI DI RISPOSTA ALLA TERAPIA CON RITUXIMAB NELL'ARTRITE REUMATOIDE REFRATTARIA AD ANTI-TNFα

*Maurizio Benucci[1], Elisabetta Ravera[2], Gianpaolo Capurro[3], Armando Russo[3], Gianantonio Saviola[4], Emanuela Cammelli[5], Mariangela Manfredi[5]*
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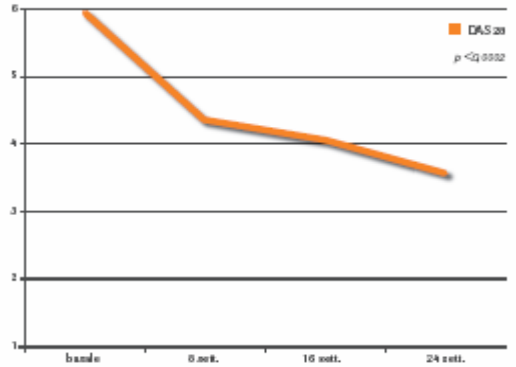
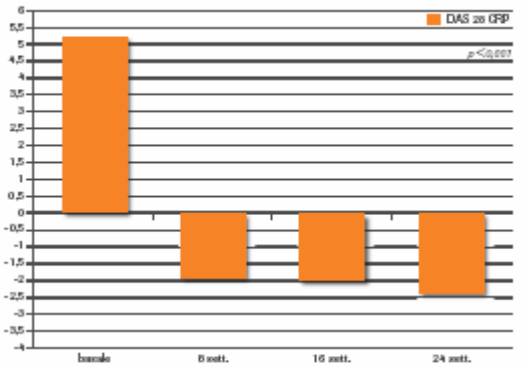
## RISULTATI-2

*Andamento del DAS 28 dopo 6 mesi dal 1° ciclo di rituximab*



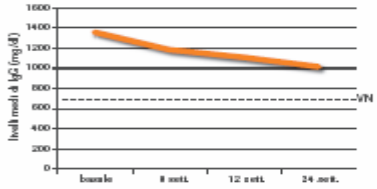

## RISULTATI-3

*Diminuzione media del del DAS 28-PCR dopo 6 mesi dal 1° ciclo di rituximab*

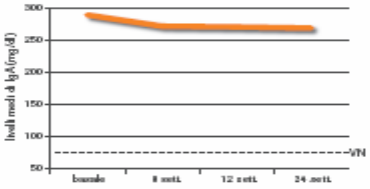



## SAFETY-1 *Andamento Ig*

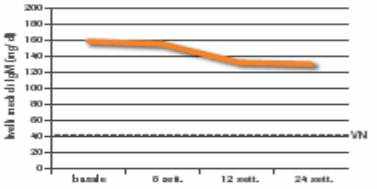
**Andamento dei livelli delle IgG dopo trattamento con rituximab**




**Andamento dei livelli delle IgA dopo trattamento con rituximab**




**Andamento dei livelli delle IgM dopo trattamento con rituximab**




## SAFETY-2

- Rituximab è stato ben tollerato ed ha registrato solo una reazione infusionale con sintomatologia simil influenzale ed una ipotensione di grado lieve, peraltro risolta con proseguimento del trattamento
- Il livello medio di Immunoglobuline è rimasto sempre al di sopra dei valori soglia per tutto il periodo di osservazione

# Long term safety data from extended follow-up and repeat use of rituximab in rheumatoid arthtritis

Ronald F Van Vollenhoven, Paul Emery,
Clifton Bingham, Edward Keystone, Maria Greenwald,
Larry W Moreland, Marianne Sweetser, Karen Rowe,
Bridget Wagner, Fabio Magrini

# Objective and methods

Objective

- To evaluate the long-term safety of multiple courses of rituximab in patients with active RA

Methods

- A further safety analysis of patients exposed to rituximab in the ongoing clinical programme was performed
  - Patients participated in Phase IIa, Phase IIb (DANCER) or Phase III (REFLEX) studies
- The current analysis includes data on all patients receiving up to 4 treatment courses

# Repeated treatment courses with rituximab

| Course | October 2005 (n) | September 2006 (n) |
|---|---|---|
| 1st Course | 1039 | 1053 |
| 2nd Course | 570 | 684 |
| 3rd Course | 191 | 400 |
| 4th Course | 40 | 142 |
| 5th Course | - | 41 |
| 6th Course | - | 11 |
| 7th Course | - | 1 |

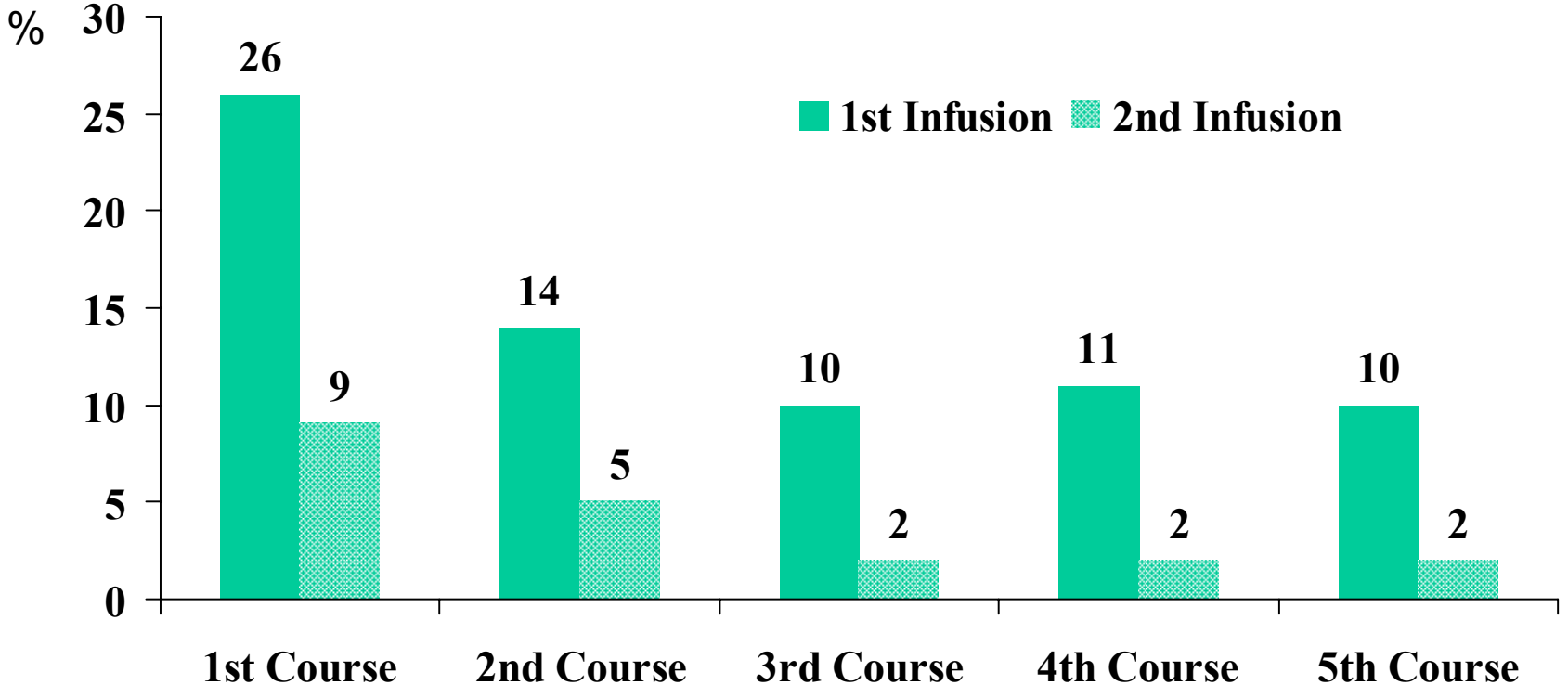
# Duration of rituximab exposure

| Duration of observation | October 2005 (n) | September 2006 (n) |
|---|---|---|
| Total (any duration) | 1039 | 1053 |
| >6 months | 987 | 1014 |
| >1 year | 839 | 957 |
| >2 years | 139 | 701 |
| >3 years | 89 | 120 |
| **Total exposure (patient-years)** | **1669 patient-years** | **2438 patient-years** |

# Rates of adverse events by treatment course

| | 1st Course (n=1053) | 2nd Course (n=684) | 3rd Course (n=400) | 4th Course (n=142) |
|---|---|---|---|---|
| Exposure pt-yrs) | 1362.89 | 717.3 | 268.11 | 73.97 |
| AEs (%) | 88% | 81% | 72% | 65% |
| Rate/100 pt-yrs | 328.9 | 296.8 | 344.3 | 342.0 |
| erious AEs | 18% | 15% | 10% | 3% |
| %) | 19.15 | 20.21 | 20.89 | 6.76 |
| Rate/100 pt-yrs | | | | |
| AEs leading to withdrawal | 3% | 2% | <1% | <1% |

# Incidence of acute infusion reactions* by treatment course of rituximab

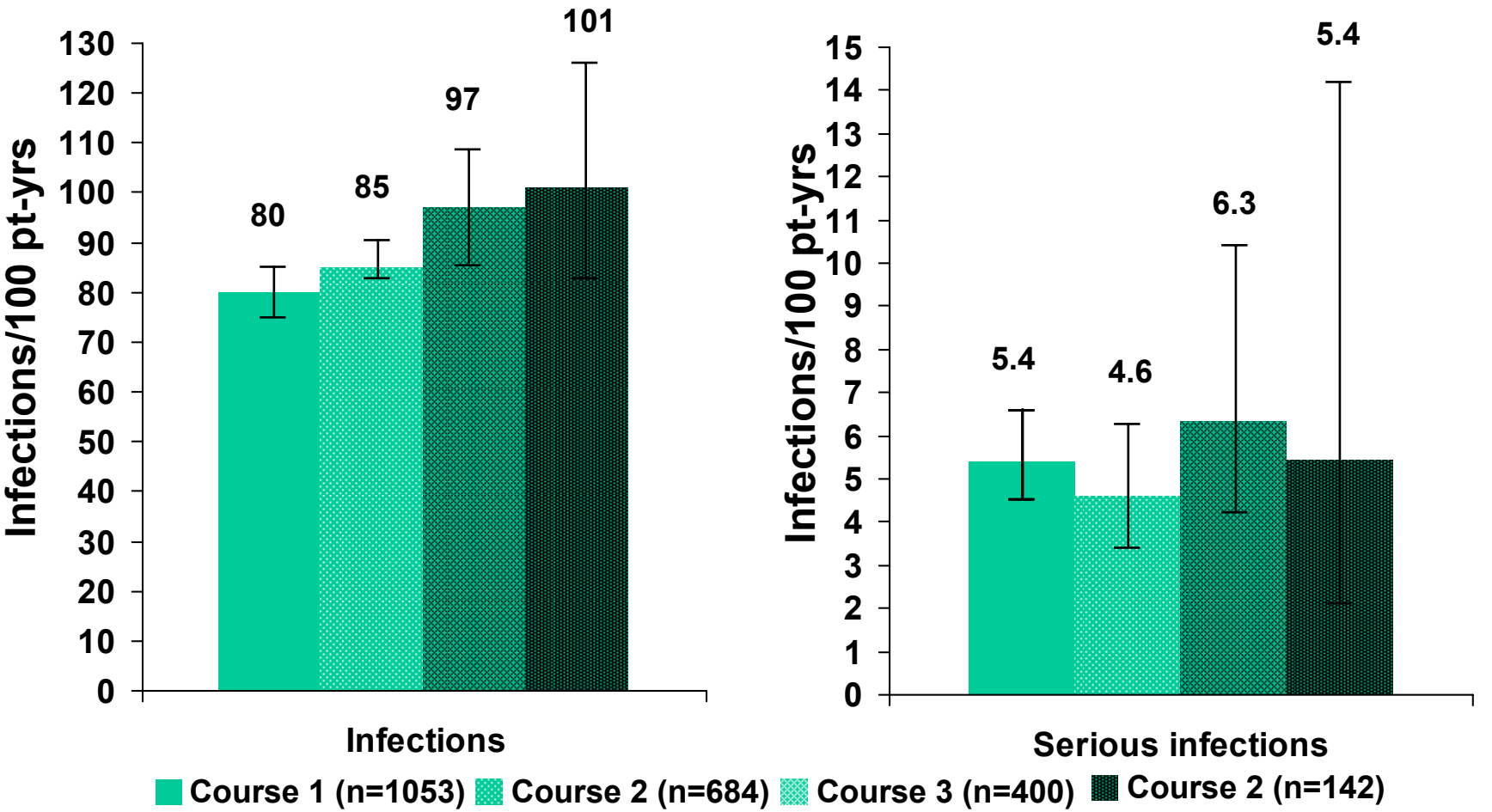



*Defined as pruritus, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic oedema, throat irritation, cough, bronchospasm, hypotension, or hypertension

# Incidence of infections

- A total of 702 patients (67%) experienced ≥1 infection
- The most common infections were upper respiratory tract infections, including nasopharyngitis (32%), and urinary tract infections (11%)
- No opportunistic infections, viral reactivations or tuberculosis were observed

# Infections/100 patient-years by treatment course



# Serious infection rate by IgM level

| | All exposure<br><br>n=1053 | Patients with normal IgG and IgM<br><br>n=761 | Patients with low IgM at any time<br><br>n=261 |
|---|---|---|---|
| **Patients with low Ig at anytime, n (%)** | - | - | **261/1053 (24.7%)** |
| **Patients with a serious infection (SI)*, n (%)** | **104 (9.9%)** | **66 (8.7%)** | **32 (12.3%)** |
| **Rate of SI per 100 patient years (95% CI)** | **5.4 (4.53, 6.38)** | **4.9 (3.93, 6.06)** | **6.4 (4.74, 8.68)** |

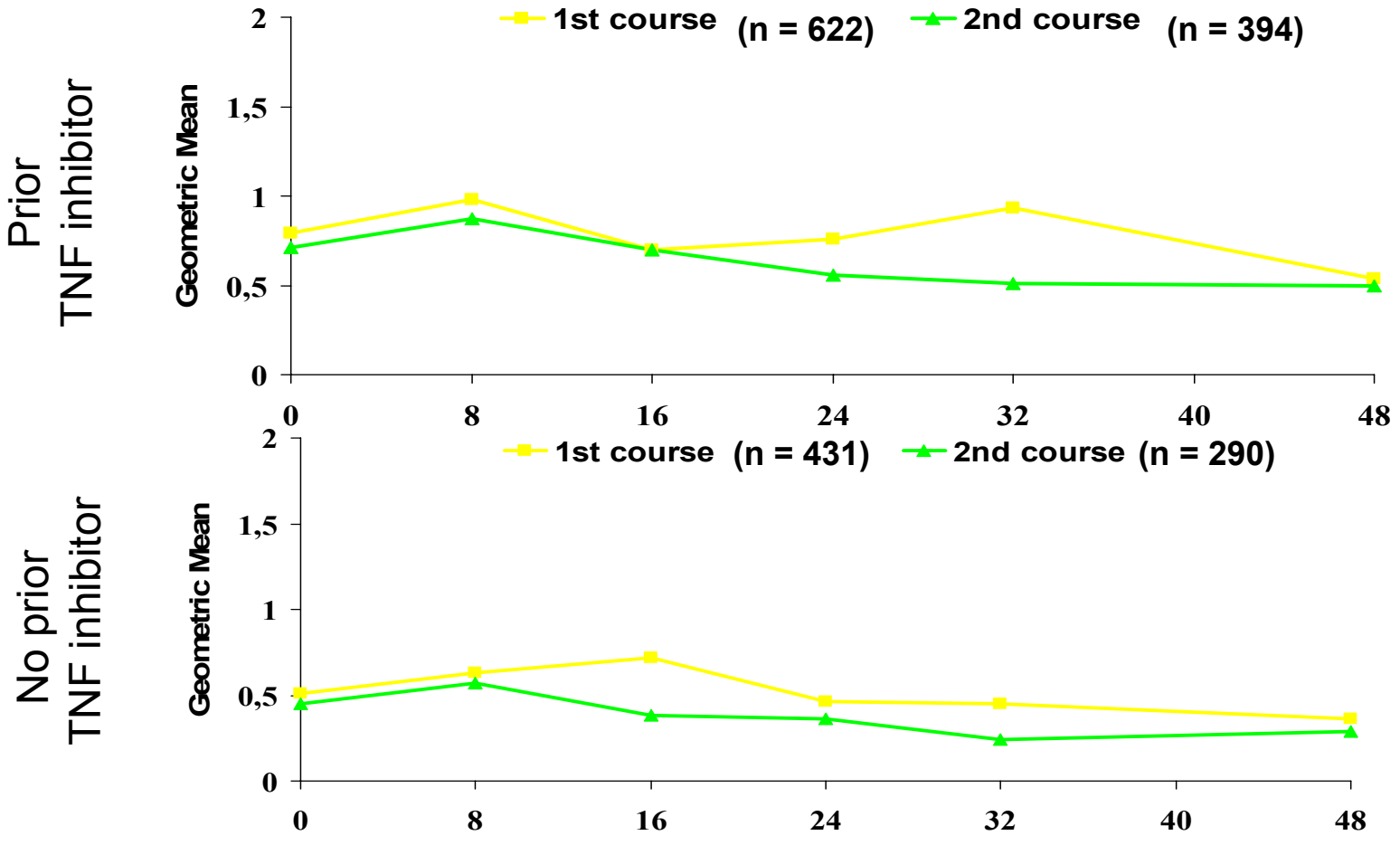
*Defined as a serious AE and/or requiring iv antibiotics

# Serious infection rate by IgG level

| | All exposure<br><br>n=1053 | Patients with normal IgG and IgM<br><br>n=761 | Patients with low IgG at any time<br><br>n=67 |
|---|---|---|---|
| **Patients with low Ig at anytime, n (%)** | - | - | **67/1053 (6.3%)** |
| **Patients with a serious infection (SI)*, n (%)** | **104 (9.9%)** | **66 (8.7%)** | **12 (17.9%)** |
| **Rate of SI per 100 patient years (95% CI)** | **5.4 (4.53, 6.38)** | **4.9 (3.93, 6.06)** | **6.8 (4.03, 11.49)** |

*Defined as a serious AE and/or requiring iv antibiotics

# Tetanus Ab titre: change over time and by treatment course



Oren S Ann Rheum Dis. 2008 Dec 4 Epub ahead of print

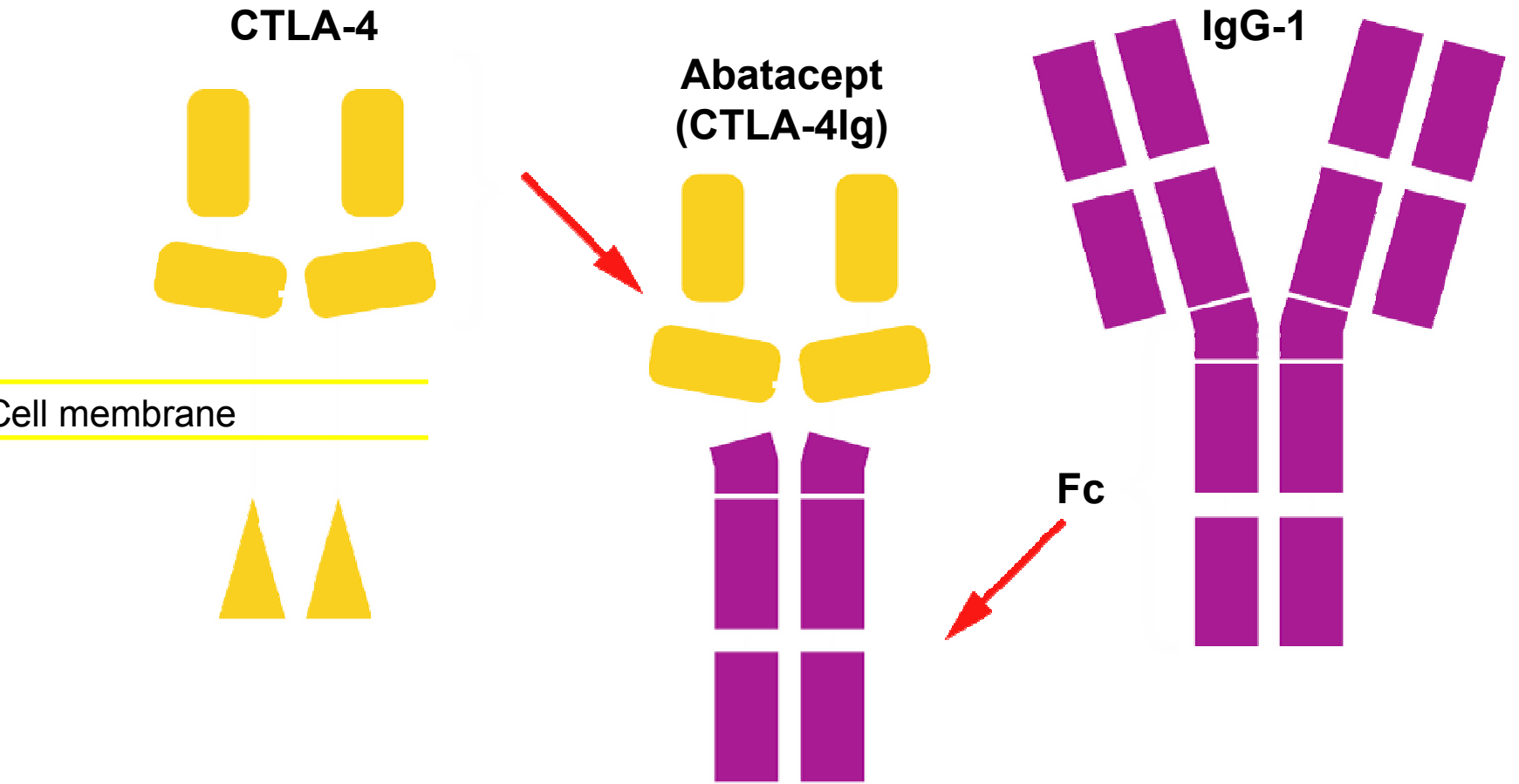
# Vaccination against influenza in rheumatoid arthritis patients: the effect of rituximab o the humoral response.

OBJECTIVE: To assess the effect of rituximab on the efficacy and safety of influenza virus vaccine in patients with rheumatoid arthritis (RA). METHODS: The study population comprised RA patients treated with conventional disease modifying drugs with or without rituximab. Split-virion inactivated vaccine containing 15 mcg hemagglutinin/dose of B/Shanghai/361/02 (SHAN), A/New Caledonia A/New Caledonia/ 20/99 (NC) (H1N1) and A/California/7/04 (CAL) (H3N2) was used. Disease activi was assessed by number of tender and swollen joints, morning stiffness duration, and evaluation of pai on the day of vaccination and 4 weeks later. CD19 positive cell levels were assessed in rituximab treated patients. Hemagglutination inhibition (HI) antibodies were tested and response was defined as >4-fold rise 4 weeks post vaccination or seroconversion in patients with a non-protective baseline leve of antibodies (<1/40). Geometric mean titers (GMT) were calculated in all subjects. RESULTS: The participants were divided into 3 groups: RA (n=29, aged 64+/-12 years), rituximab-treated RA (n=14, aged 53+/-15 years) and healthy controls (n=21, aged 58+/-15 years). All baseline protective levels of HI antibodies and GMT were similar. Four weeks after vaccination, there was a significant increase in GMT for NC and California antigens in all subjects, but not for the Shanghai antigen in the rituximab group. In Rituximab treated patients,, the percentage of responders was low for all three antigens teste achieving statistical significance for California antigen. Parameters of disease activity remained unchanged. CONCLUSION: Influenza virus vaccine generated a humoral response in all RA study patients and controls. Although the response was significantly lower among rituximab-treated patients treatment with rituximab does not preclude administration of vaccination against influenza.

# Malignancies

- A total of 36 high- and low-grade malignancies (18 in C1, 13 in C2, 4 in C3 and 1 in C4) occurred in 32 pts (3%), of which 4 had a fatal outcome (duodenal cancer, adenocarcinoma, pancreatic cancer, myelodysplastic syndrome)
- No lymphoproliferative malignancies and no increased risk of malignancy with additional courses of treatment were observed

# Abatacept (CTLA-4Ig) is a Recombinant Fusion Human Protein Comprised of CTLA-4 and a Modified Fc Domain of IgG-1

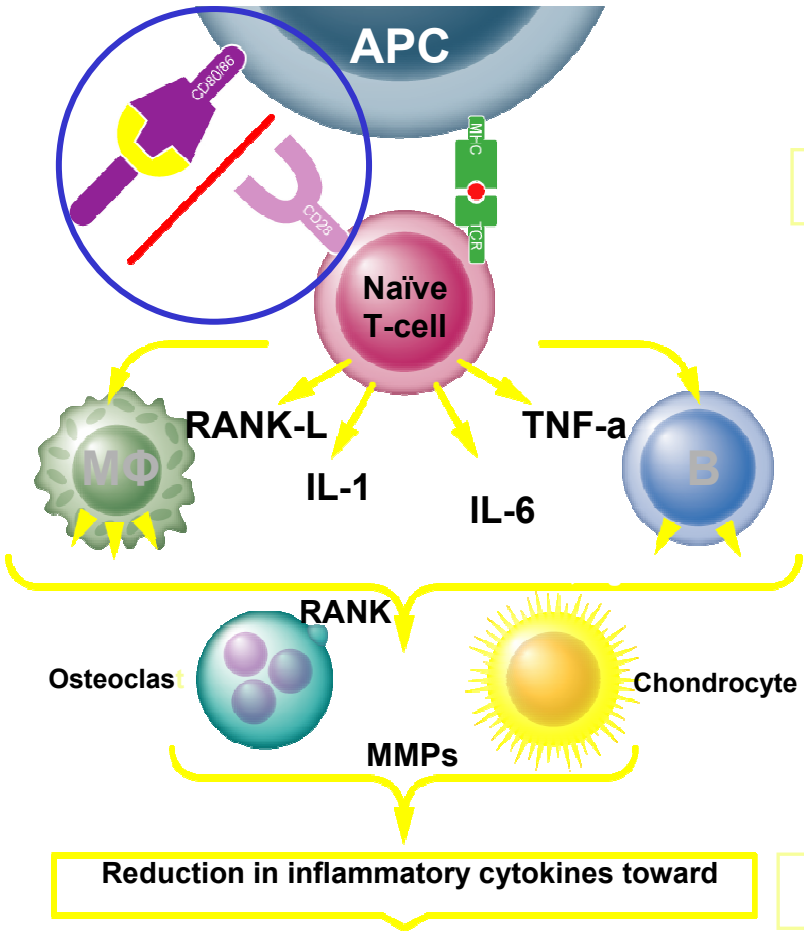



Linsley PS et al. J Exp Med 1991; 174: 561–9; Ig=immunoglobulin.

# Abatacept: Normalizing Aberrant Immune Responses

Decrease T-cell activation and proliferation

Decrease pro-inflammatory cytokine secretion from activated synovial macrophases




Upstream modulation

Decrease autoantibody production (e.g. RF) reduces clonal expansion

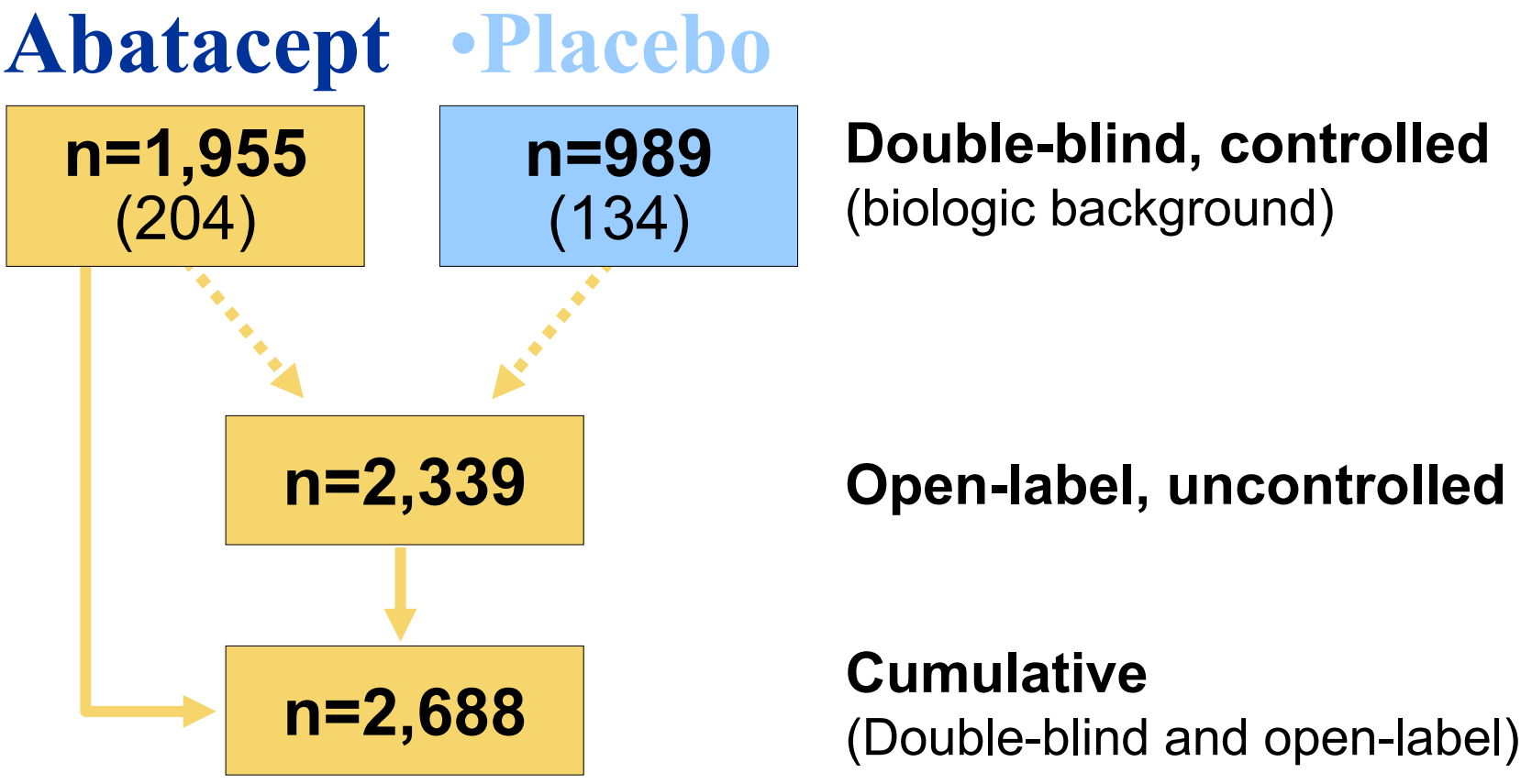
Downstream impact

Adapted from Choy EH and Panayi GS. N Engl J Med. 2001; 344: 907–16 and from Linsley PS et al. J Exp Med. 1991; 174: 561–9.

# Therapeutic Indication

- Abatacept in combination with methotrexate is indicated for
  the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other disease-modifying anti-rheumatic drugs including at least one tumour necrosis factor (TNF) inhibitor.
- A reduction in the progression of joint damage and improvement of physical function have been demonstrated during combination treatment with Abatacept and methotrexate.

# RA Safety Population



# Overview of Patients with Adverse Drug Reactions Double-blind, Controlled Study Periods as of June 05

| | Number (%) of patients | |
|---|---|---|
| | Abatacept n=1955 | Placebo n=989 |
| Adverse Drug Reactions (ADR) | 1020 (52.2) | 456 (46.1) |
| Serious ADR | 61 (3.1) | 17 (1.7) |
| Discontinuation due to ADR | 67 (3.4) | 22 (2.2) |
| Deaths | 1 (<0.1) | 2 (0.2) |

EU abatacept SmPC; EPAR; http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4170-Slide-Index.htm, accessed 1

# Serious ADRs of Infections (≥ 0.1%)
# Double-blind, Controlled Study Periods

| Preferred term | Number (%) of patients | |
|---|---|---|
| | Abatacept n=1955 | Placebo n=989 |
| **Patients with Serious ADR infections** | 36 (1.8) | 10 (1.0) |
| Pneumonia | 6 (0.3) | 3 (0.3) |
| Cellulitis | 3 (0.2) | 2 (0.2) |
| Localised infection | 3 (0.2) | 0 |
| Urinary tract infection | 2 (0.1) | 1 (0.1) |
| Bronchitis | 2 (0.1) | 0 |
| Diverticulitis | 2 (0.1) | 0 |
| Pyelonephritis acute | 2 (0.1) | 0 |

EU Orencia SmPC, EPAR, FDA website

# Serious Infections in the RA Abatacept Clinical Development Programme Compared to that in RA Cohorts

- 6 RA cohorts (ever exposed to DMARDs):
  - British Columbia RA Cohort (Canada)
  - Norfolk Arthritis Registry (UK)
  - National Data Bank for Rheumatic Diseases (US)
  - Inpatient Register RA cohort (Sweden)
  - Early Arthritis Register cohort (Sweden)
  - PharMetrics medical and pharmacy claims database (US)

Simon T et al. Ann Rheum Dis 2007; 66 (S11): 438.

# Methods: Data Sources
# Characteristics of RA DMARDs Cohorts

| Data source | BC | PharMetrics | NOAR | NDB | Swedish ERA | Swedish Inpatient* |
|---|---|---|---|---|---|---|
| Data type | Claims | Claims | Questionnaire and assessment | Questionnaire | Claims and assessment | Claims and assessment |
| Time covered | 1996–2001 | 1998–2002 | 1990–1999 | 1998–2003 | 1994–2003 | 1990–2003 |
| Population | 12,337 | 52,444 | 523 | 10,499 | 3,703 | 53,067 |
| Follow-up Mean (yrs) | 4.9 | 1.7 | 7.9 | 3.3 | 3.6 | 5.6 |
| Age (%) | | | | | | |
| <44 years | 25 | 30 | 21 | 14 | 21 | 9 |
| 45 to 74 | 64 | 67 | 70 | 72 | 65 | 56 |
| ≥75 | 11 | 3 | 9 | 14 | 14 | 35 |
| Female (%) | 72 | 75 | 68 | 76 | 70 | 71 |

Simon T et al. Ann Rheum Dis 2007; 66 (S11): 438.

May include a small percentage of RA patients who had never

# Serious Infections in the Rheumatoid Arthritis Abatacept Clinical Development Program: An Updated Epidemiological Assessment

| IRs of infections (events/100 person-years) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Cohort IR (95% CI) | Abatacept trial pop* | Norfolk arthritis ^ | Early RA registry^ | British Columbia^ | National data bank^ | Inpatient register RA^ | Pharmetrics^ |
| Hospitalized infection | 2.72 (2.37; 3.10) | 1.41 (1.18; 1.69) | 1.83 (1.57; 2.15) | 3.00 (2.65; 3.40) | - | 3.92 (3.52; 4.37) | 3.53 (3.53; 3.96) |
| Hospitalized pneumonia | 0.65 (0.47; 0.82) | 0.27 (0.18; 0.40) | 0.53 (0.39; 0.71) | 0.79 (0.62; 1.01) | 1.31 (1.09; 1.58) | 1.04 (0.84; 1.28) | 1.26 (1.04; 1.53) |

*Observed IR. ^expected IR. IR =incidence rate

Simon TA et al. Ann Rheum Dis. 2007; 66(S11) :438

# Tuberculosis in Abatacept Clinical Trial Program

- Exclusion criteria in clinical trials:
  - **Pivotal Phase II and III studies (AIM[1], ATTAIN[2], ASSURE[3], ATTEST[4])**
    - **Exclusion of patients with a history of active TB during the previous 3 years before entry**
    - **Patients were screened for latent TB using skin testing**
    - **Patients with evidence of possible latent TB who had not received adequate chemoprophylaxis were excluded**
  - **Phase IIIb study (ARRIVE[5])**
    - **Subjects PPD+ at screening could be enrolled if they had treatment for latent TB and had a negative chest x-ray at enrollment**
- **Observed cases of Tuberculosis in all pivotal studies [6]**
  - **2 cases of presumed TB in abatacept treated patients**
  - **1 case of presumed TB in the placebo arm**
  - **2 cases of confirmed tuberculosis with Infliximab – ATTEST trial**

remer JM et al. Annals of Internal Med 2006;144: 865–76; [2]Genovese MC et al N Engl J Med 2005; 144: 865–76; [3]Weinblatt M et al thritis Rheum 2006; 54(9): 2807–16; 4. Schiff M et al. Abstract accepted at ACR 2006, L43[5]M Schiff et al Annals Rheum s:2007;66(S11) : 89; 6. http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4170-Slide-Index.htm

# Infections: Conclusions

- **Abatacept treatment associated with an incidence of infection and serious infection modestly increased over placebo of respectively 23.2% vs 19.5% and 1.8% vs 1%.**
- **Treatment with abatacept should not be initiated in patients with active infections until infections are controlled.**
- **Screening for latent tuberculosis and viral hepatitis should be performed in accordance with published guidelines before starting therapy with abatacept.**

# Malignancies
# Double-blind, Controlled Study Periods

| Type of malignancy | Number (%) of patients | |
|---|---|---|
| | Abatacept n=1955 | Placebo n=989 |
| Total | 27 (1.4) | 11 (1.1) |
| Non-melanoma skin | 16 (1.0) | 6 (0.6) |
| Basal cell carcinoma | 11 (0.6) | 4 (0.4) |
| Squamous cell carcinoma | 6 (0.3) | 2 (0.2) |
| Solid | 9 (0.5) | 5 (0.5) |
| Lung | 4 (0.2) | 0 |
| Thyroid | 2 (0.1) | 0 |
| Breast | 1 (<0.1) | 2 (0.2) |
| Prostate | 1 (<0.1) | 0 |
| Bladder | 1 (<0.1) | 0 |
| Renal | 1 (<0.1) | 0 |
| Endometrial/uterine | 0 | 2 (0.2) |
| Melanoma | 0 | 1 (0.1) |
| Hematologic | 2 (0.1) | 0 |
| Lymphoma | 1 (<0.1) | 0 |
| Myelodysplastic syndrome | 1 (<0.1) | 0 |

# Malignancies – Abatacept: Double-blind and Cumulative Study Periods

| Type of malignancy incidence rate | Double-blind n=1955 (p-y=1688) per 100 p-y | Through Jun 2005 n=2688 (p-y=4764) per 100 p-y |
|---|---|---|
| Non-melanoma Skin | 0.89 | 0.63 |
| Solid | 0.53 | 0.55 |
| Lung | 0.24 | 0.21 |
| Thyroid | 0.12 | 0.05 |
| Breast | 0.06 | 0.05 |
| Prostate | 0.06 | 0.05 |
| Bladder | 0.06 | 0.03 |
| Renal | 0.06 | 0.03 |
| Ovarian | 0 | 0.05 |
| Melanoma | 0 | 0.03 |
| Endometrial / Uterine | 0 | 0.05 |
| Cervix | 0 | 0.03 |
| Hematologic | 0.12 | 0.13 |
| Lymphoma | 0.06 | 0.10 |
| Myelodysplastic Syndrome | 0.06 | 0.03 |

# Literature Malignancy Conclusion

- In RA patients, increased risk for lymphoma and lung cancer and decreased risk for colorectal cancers compared with non-RA or general population

- Factors that may contribute to increased risk of lymphoma and lung cancer: selected study population, smoking, viral infection, severity of RA, RA treatments or other factors

- Further studies may be needed to investigate the underlying mechanisms for the increased or decreased risk of specific cancers in RA

Smitten AL et al. Ann Rheum Dis 2006; 65 (Suppl II): 488.

# Comparison of Abatacept Clinical Trial Experience to the General Population

- **Objectives:**
  - **To compare the malignancy experience in the RA abatacept clinical development programme with that observed in the general population (FDA requirement)**
  - **To determine whether the malignancy SIRs obtained were consistent with those seen in the published literature comparing other RA populations to non-RA or general populations**

Simon T et al. Arthritis Rheum 2007; 56 (9S): S345.

# Comparison of Abatacept Clinical Trial Experience to the RA Cohorts

- Objective:
  - To determine if the observed number of malignancy cases in the abatacept cumulative clinical trial experience was similar to the number expected based on incidence rates of malignancy in cohorts of RA patients treated with DMARDs

Simon T et al. Annals Rheum Dis 2007; 66(S11): 90.

# Methods: Exposures and Malignancies

- Exposure
  - RA DMARD Cohorts
    - Person–time from the first DMARD exposure until the first event or the end of follow-up, whichever occurred first
  - Abatacept Trial Experience
    - Person–time exposure to abatacept until the first event or end of treatment + 56 days, whichever occurred first
- Malignancies
  - Total malignancy excluding non-melanoma skin cancer
  - Lymphoma
  - Lung cancer
  - Breast cancer

Simon T et al. Annals Rheum Dis 2007; 66 (S11): 90.

# Incidence Rates of Malignancies in Abatacept Trials

| | Incidence Rate/100 py (95% CI) | | |
|---|---|---|---|
| | DB* Placebo n=989 | DB* Abatacept n=1955 | Cumulative† n=4134 |
| Total exposure (person–years) | 794 | 1688 | 8388 |
| Total malignancies (excluding non-melanoma skin) | 0.63 (0.26, 1.5) | 0.59 (0.32, 1.1) | 0.61 (0.45, 0.80) |
| Lymphoma | 0 | 0.06 (0.01, 0.43) | 0.06 (0.02, 0.14) |
| Lung cancer | 0 | 0.24 (0.09, 0.64) | 0.15 (0.08, 0.27) |
| Colo-rectal | 0 | 0 | 0.02 (0.00, 0.09) |
| Breast cancer | 0.25 (0.06, 1.01) | 0.06 (0.01, 0.43) | 0.08 (0.03, 0.17) |

Simon T et al. Annals Rheum Dis 2007; 66 (S11): 90

# Malignancy Summary

- In carcinogenicity studies in mice, an increase in lymphomas and mammary tumours were noted. The clinical significance of this observation is unknown.
- Patients with known malignancies not included in abatacept clinical trials.
- In double blind and cumulative study periods
  - Frequency similar to placebo and RA population overall and for major categories (skin, solid, hematological)
  - For lymphoma and lung cancer, incidence within reported ranges for RA patients. Clinical presentation and incidence over time, do not suggest increased risk with abatacept.
- The potential role of abatacept in the development of malignancies, including lymphoma, in humans is unknown.
- Risk management plan will provide further information to better define risk of malignancy.

Simon T et al; Annals Rheum Dis 2007;66(S11) :90

# Acute Infusional Events*

| Acute* infusional adverse events | Abatacept (n=1650) (%) | Placebo (n=834) (%) |
|---|---|---|
| Total patients with acute infusion reactions | 9.8 | 6.7 |

- Hypersensitivity reactions* (in studies AIM, ATTAIN and ASSURE)
- Less than 1% of patients experienced hypersensitivity reactions, including two cases of anaphylaxis or anaphylactoid reactions.
- Other events potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in less than 0.9% of patients treated with Abatacept and generally occurred within 24 hours of an infusion with abatacept.
- Appropriate medical support measures for the treatment of hypersensitivity reactions should be available.

J Sm PC; Sibilia J et al. Clin Exp Rheumatol 2007; 25 (5 Suppl 46): S46–56.

# Autoimmune Events During Double-blind and Open-label Periods

| | Double-blind period | | Open-label period |
|---|---|---|---|
| | Abatacept (n=1650) n | Placebo (n=834) n | All patients (n=2688) (%) |
| **Auto-immune events** | 28 | 8 | 1.9 |
| **Psoriasis** | 9 | 0 | 0.7 |
| **Guttate psoriasis** | 1 | 0 | 0.06 |
| **Vasculitis** | 5 | 2 | 0.3 |
| **Lupus like syndrome** | 2 | 0 | 0.12 |

Sibilia J et al. Clin Exp Rheumatol 2007; 25 (5 Suppl 46): S46–56.

# Immunogenicity

- **Overall incidence of anti-abatacept antibody responses was 2.8% (62/2237) in patients treated for up to 3 years with abatacept.**
- **In patients assessed for antibodies at least 56 days after discontinuation of abatacept, incidence of immunogenicity was 7.4% (15/203).**
- **There was no apparent correlation of antibody development to clinical response or adverse event based on this limited dataset of patients with antibodies.**

# Vaccination Recommendations in Patients Treated with abatacept

- **Based on its mechanism of action, abatacept may blunt the effectiveness of some immunizations.**
- **Live vaccines should not be given concurrently with abatacept**
  **or within 3 months of its discontinuation.**
- **No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving abatacept.**
- **The efficacy of vaccination in patients receiving abatacept is not known.**

# Use of abatacept during Pregnancy

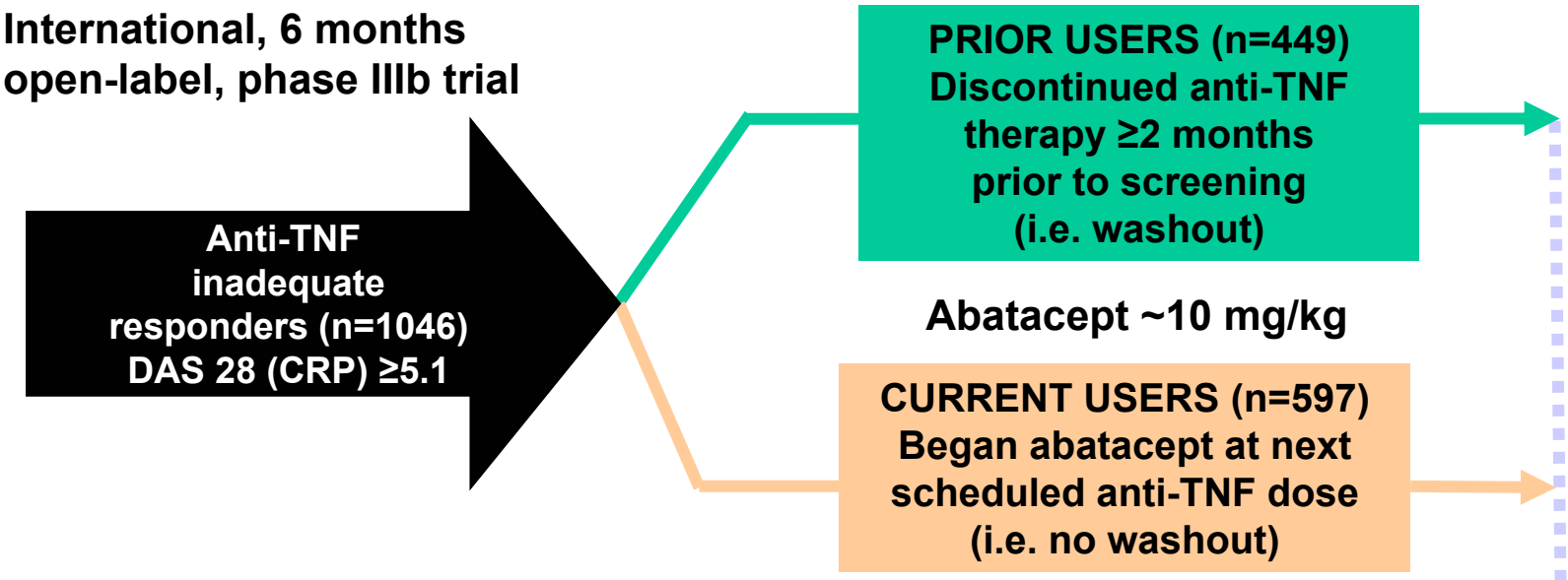
- **There are no adequate data from use of abatacept in pregnant women.**
- **In embryo-foetal development studies no undesirable effects were observed at doses up to 29-fold a human 10 mg/kg dose based on AUC.**
- **In a pre- and postnatal development study limited changes in immune function were observed at 11-fold a human 10 mg/kg dose based on AUC**

# Safety of Abatacept in Patients with Active Rheumatoid Arthritis and intolerance and/or an Inadequate Response to Anti-TNF Therapy:

Results from the ARRIVE (**A**batacept **R**esearched in **R**heumatoid Arthritis Patients with an **I**nadequate Anti-TNF Response to **V**alidate **E**ffectiveness) Trial

Schiff M et al. Arthritis Rheum 2007; 56 (9S): 391.

# Study Design




**To present clinical safety and tolerability data from 1046 patients with active RA and an inadequate response to ≥3 months of anti-TNF therapy and who were switched to abatacept**

**Abatacept (~10 mg/kg, according to weight range) was administered on Days 1, 15 and 29, and then every 28 days thereafter, +/– stable background non-biologic DMARD therapy.**

**Adapted from Schiff M et al. Arthritis Rheum 2007; 56 (9S): 391.**

# Overview of Safety Through Days1–169

| N (%) | Prior users (n=449) | Current users (n=597) | Overall (n=1046) |
|---|---|---|---|
| Total patients with AEs | 350 (78.0) | 473 (79.2) | 823 (78.7) |
| Total infections | 176 (39.2) | 231 (38.7) | 407 (38.9) |
| Discontinuations due to AEs | 17 (3.8) | 24 (4.0) | 41 (3.9) |
| SAEs | 50 (11.1) | 59 (9.9) | 109 (10.4) |
| Total serious infections | 12 (2.7) | 13 (2.2) | 25 (2.4) |
| Neoplasms | 8 (1.8) | 7 (1.2) | 15 (1.4) |
| Discontinuations due to SAEs | 9 (2.0) | 8 (1.3) | 17 (1.6) |

Schiff M et al. Arthritis Rheum 2007; 56 (9S): 391.

# Overview of Serious Infections Days 1–169

| Infections | Prior users (n=449) n (%) | Current users (n=597) n (%) | Overall (n=1046) |
|---|---|---|---|
| Total serious infections | 12 (2.7) | 13 (2.2) | 25 (2.4) |
| Pneumonia | 0 | 4 (0.7) | 4 (0.4) |
| Bronchitis | 2 (0.4) | 1 (0.2) | 3 (0.3) |
| Lobar pneumonia* | 2 (0.4) | 0 | 2 (0.2) |

Schiff M et al. Arthritis Rheum 2007; 56 (9S): 391.

# Conclusions

- In a 6 month-open label study, in patients with either intolerance or IR to 1–3 anti-TNF therapy, directly switched to abatacept, abatacept on background therapy with DMARD(s) showed
  - A comparable safety profile to the ATTAIN trial
  - Improvements in disease activity as assessed by DAS 28-derived criteria
- These results extend previous findings from the ATTAIN study in patients with IR to 1–2 anti-TNF therapy
- Our findings support the direct switch from anti-TNF agents to abatacept in clinical practice

Schiff M et al. Arthritis Rheum 2007; 56 (9S): 391

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