23ème Congrès Français de Rhumatoliogie
Paris, 30 Novembre 2010

Efficacité et tolérance des traitements de la polyarthrite rhumatoïde étudiés par méta-analyse hiérarchique bayésienne. Combinaison simultanée des résultats relevés dans les essais randomisés et les études observationnelles avec groupe contrôle

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METHODES

Typologies des Revues Systématiques

Revue Systématique qualitative

- Cerner la question posée
- Expliciter les critères d'éligibilité : PICOT Population, intervention, comparateurs, outcome, durée
- Choisir les bases documentaires à exploiter
- Identifier les articles pertinents
- Apprécier la qualité des études (validité interne-externe)

Extraction des données selon une grille standardisée

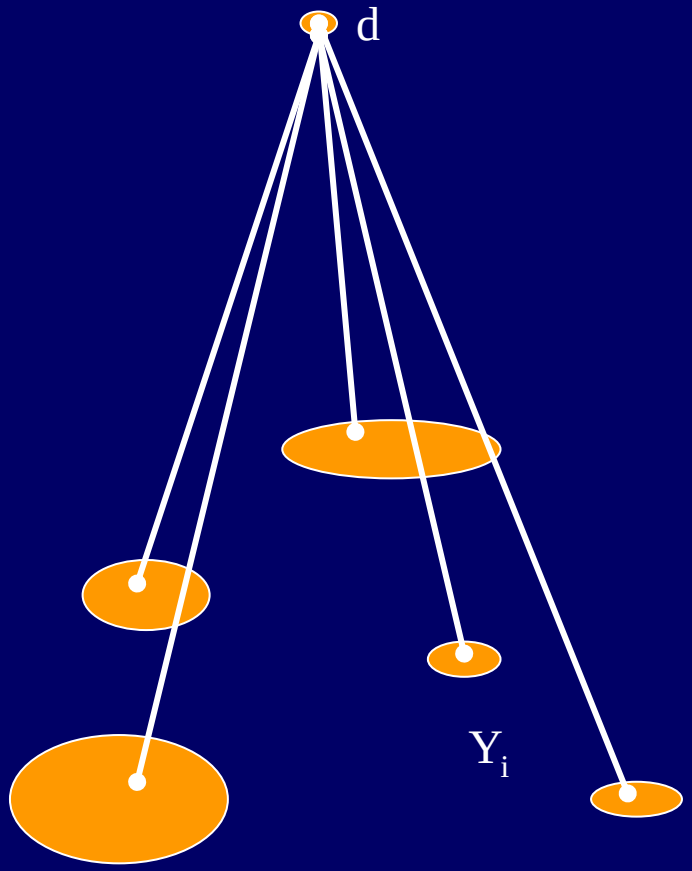
- Tables de données probantes

Revue systématique quantitative

- Synthèse données probantes : méta, MCT
- Estimation de l'hétèrogénéité
- Neutralisation des Biais

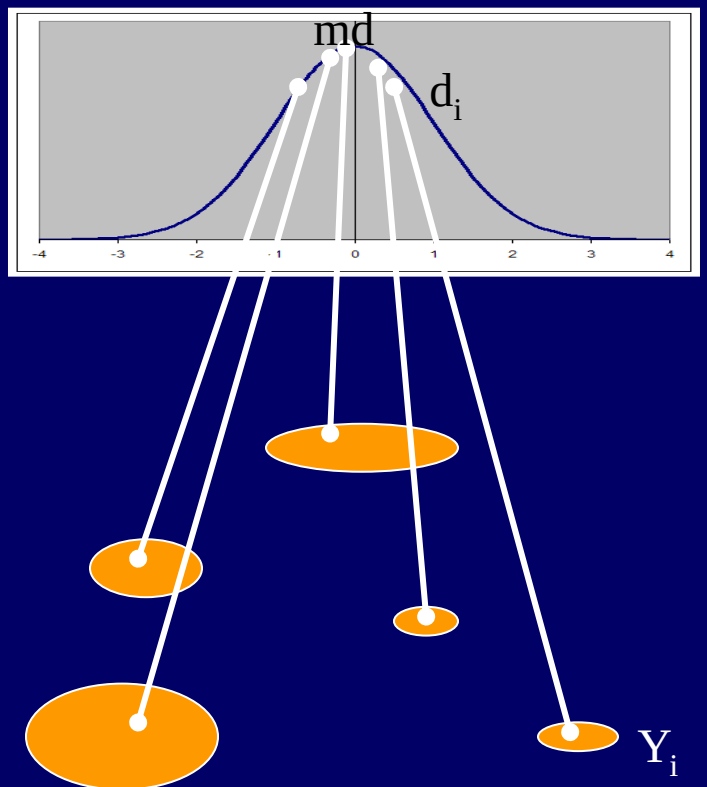
Modèles à Effets Fixes et Aléatoires

Méta à Effets fixes



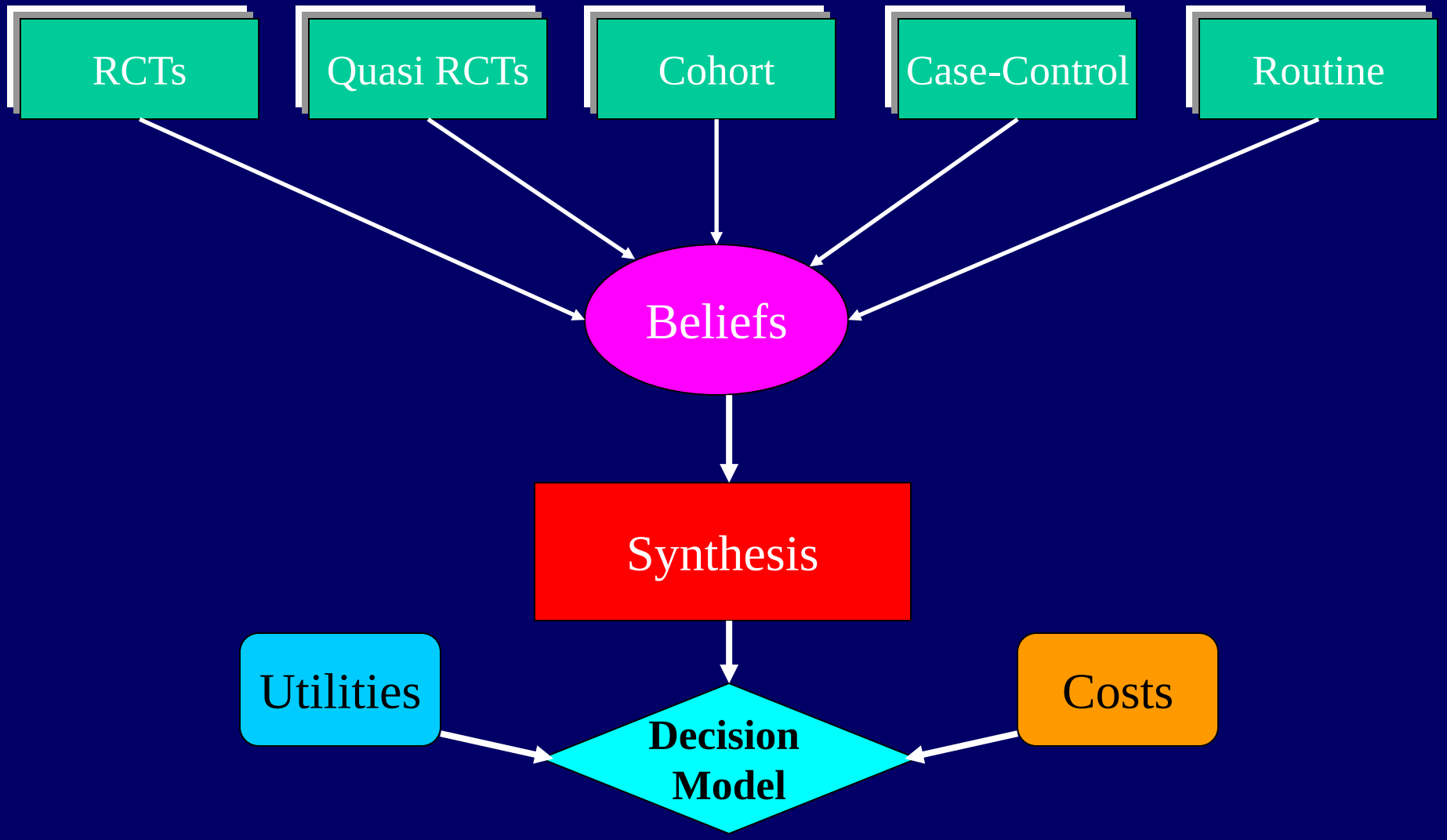
$Y_i \sim N(d, v_i^2)$, $i = 1, \ldots, k$

Méta à Effets aléatoires



$Y_i \sim N(d_i, v_i^2)$ et $d_i \sim N(md, \tau^2)$, $i = 1, \ldots, k$

Generalised Evidence Synthesis



Hierarchical Model

$$y_{ij} \sim N[\theta_{ij}, s_{ij}^2] \qquad i = 1, \ldots, n_j \;\&\; j = 1, \ldots, J$$

$$\theta_{ij} \sim N[\psi_j, \sigma_j^2]$$

$$\psi_j \sim N[\mu, \tau^2]$$

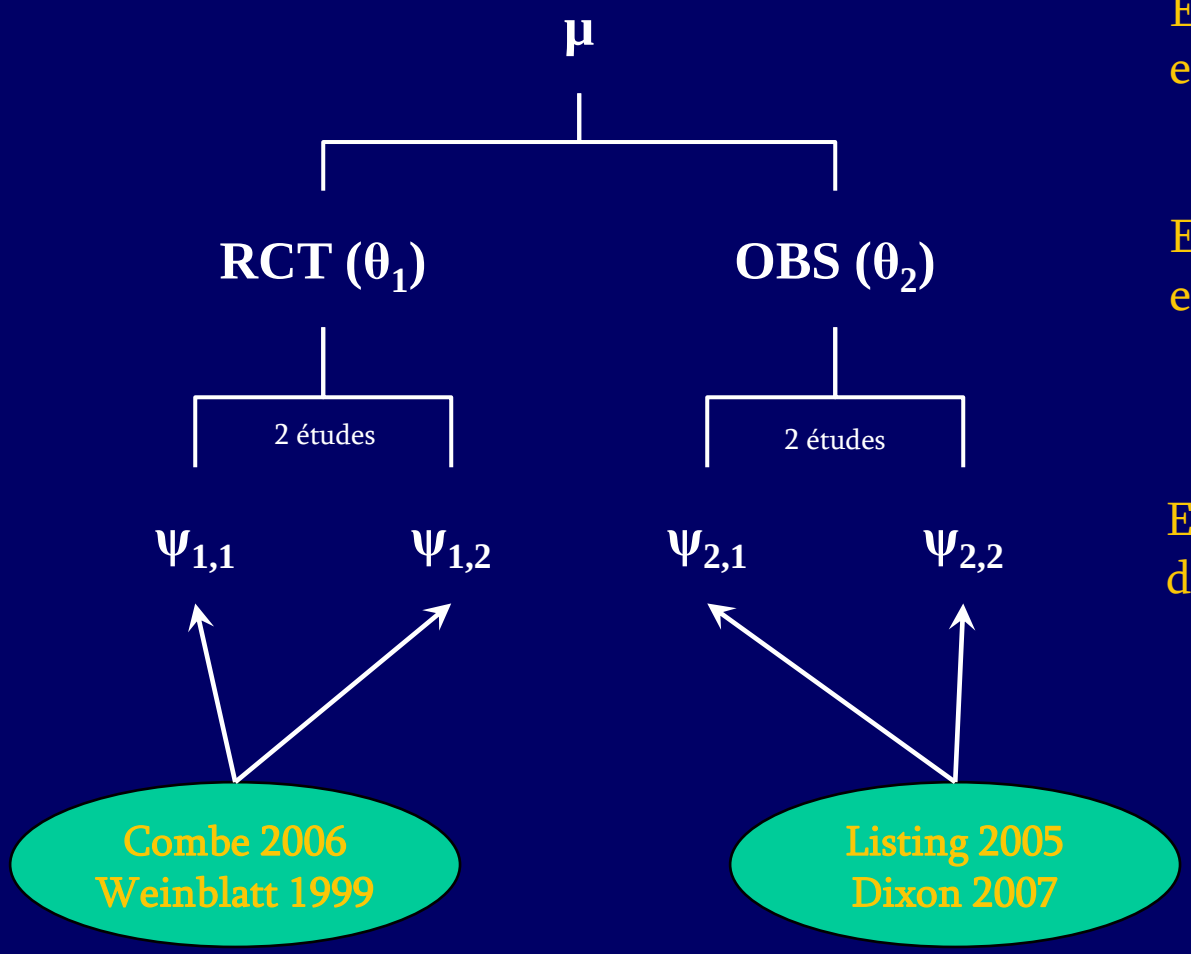
$$\mu \sim [-,-],\ \sigma_j^2 \sim [-,-] \;\&\; \tau^2 \sim [-,-]$$

Hierarchical Model - Extensions

- Inclusion of empirical assessment of (differential) bias with uncertainty, i.e. distribution
- Bias Constraint

$$\left|\psi_{RCT} - \mu\right| \leq \left|\psi_{Coh} - \mu\right| \leq \left|\psi_{CCP} - \mu\right| \leq \left|\psi_{CCH} - \mu\right|$$

Structure du Modèle Hiérarchique



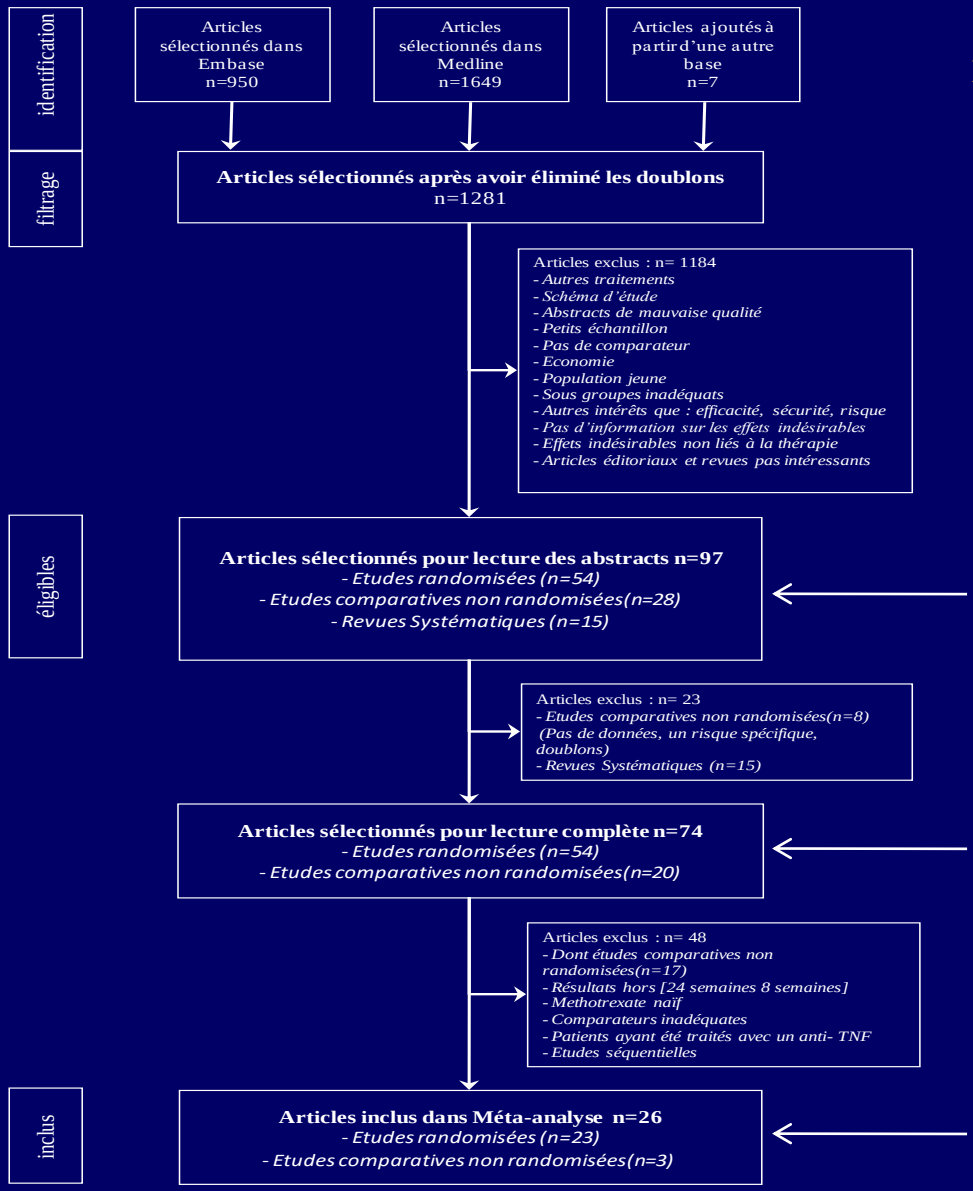
Effet commun d'Etanercept estimé dans la population

Effet commun d'Etanercept estimé par type d'étude

Effet d'Etanercept estimé dans chaque étude

RESULTATS

Arbre de Sélection PRISMA



Interrogations : Juin 2010

97 articles sélectionnés sur titre

74 articles sélectionnés sur abstract

26 articles sélectionnés sur lecture complète

RCT sélectionnés (1/2)

TTX	*N°*	*Référence*
ETA	1	Combe, B., C. Codreanu, et al. (2009). "Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study." Ann Rheum Dis 68(7): 1146-1152.
ETA	2	Combe, B., C. Codreanu, et al. (2006). "Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison." Ann Rheum Dis 65(10): 1357-1362.
ETA	3	Klareskog, L., D. Van Der Heijde, et al. (2004). "Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: Double-blind randomised controlled trial." Lancet 363(9410): 675-681.
ETA	4	Van der Heijde, D., L. Klareskog, et al. (2006). "Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial." Arthritis Rheum 54(4): 1063-1074.
ETA	5	Weinblatt ME, Kremer JM, Bankhurst AD et al. “A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate”. N Engl J Med 1999;340:253–9.
ETA	6	Moreland LW, Schiff MH,Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial, Ann Intern Med. 1999 Mar 16;130(6):478-86.
ETA	7	Van Riel, P.L.C.M., et al., Efficacy and safely of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: The ADORE study. Annals of the Rheumatic Diseases, 2006. 65(11): p. 1478-1483.
ADA	8	Furst, D. E., M. H. Schiff, et al. (2003). "Adalimumab, a Fully Human Anti-Tumor Necrosis Factor-(alpha) Monoclonal Antibody, and Concomitant Standard Antirheumatic Therapy for the Treatment of Rheumatoid Arthritis: Results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis)." Journal of Rheumatology 30(12): 2563-2571.
ADA	9	Keystone et al (2004) Radiographic, Clinical, and functinal Outcomes of treatment with adalimumab (a human anti-Tumor Necrosis Factor Monoclonal Antibody) in patients with active rheumatoid arthritis receiving concomitant Methotrexate therapy : Arth & Rheu 50(5): 1400-1411
ADA	10	Kim, H. Y., S. K. Lee, et al. (2007). "A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate." APLAR Journal of Rheumatology 10(1): 9-16.
ADA	11	Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. “Adalimumab, a fully human antitumor necrosis factor _ monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial”. Arthritis Rheum 2003;48:35-45.
ADA	12	Van De Putte, L.B.A., et al., Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Annals of the Rheumatic Diseases, 2004. 63(5): p. 508-516.
ADA	13	Miyasaka, N., Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Mod Rheumatol, 2008. 18(3): p. 252-62.
INF	14	Lipsky, P. E., D. M. F. M. Van Der Heijde, et al. (2000). "Infliximab and methotrexate in the treatment of rheumatoid arthritis." New England Journal of Medicine 343(22): 1594-1602.

RCT sélectionnés (2/2)

INF	15	Maini et al. (1999) « Infliximab (chimeric anti-tumour necrosis factor & monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate : a randomised phase III trial". Lancet 354: 1932-39
INF	16	Schiff, M., M. Keiserman, et al. (2008). "Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate." Ann Rheum Dis 67(8): 1096-1103.
INF	17	Westhovens, R., D. Yocum, et al. (2006). "The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial." Arthritis Rheum 54(4): 1075-1086.
INF	18	Zhang, F. C., Y. Hou, et al. (2006). "Infliximab versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: A preliminary study from China." APLAR Journal of Rheumatology 9(2): 127-130.
GOL	19	Kay, J., E. L. Matteson, et al. (2008). "Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study." Arthritis Rheum 58(4): 964-975.
GOL	20	Keystone, E. C., M. C. Genovese, et al. (2009). "Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study." Ann Rheum Dis 68(6): 789-796.
GOL	21	Kremer, J., C. Ritchlin, et al. (2010). "Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study." Arthritis Rheum 62(4): 917-928.
TCZ	22	Genovese, M. C., J. D. Mckay, et al. (2008). "Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study." Arthritis Rheum 58(10): 2968-2980.
TCZ	23	Smolen, J. S., A. Beaulieu, et al. (2008). "Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial." Lancet 371(9617): 987-997.
TCZ	24	Maini, R. N., P. C. Taylor, et al. (2006). "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 54(9): 2817-2829.
TCZ	25	Nishimoto, 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 randomised controlled trial of tocilizumab. Ann Rheum Dis, 2007. 66(9): p. 1162-7.
TCZ	26	Nishimoto, N., et al., Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol, 2009. 19(1): p. 12-9.
CZP	27	Keystone, E., D. Van Der Heijde, et al. (2008). "Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: Findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study." Arthritis and Rheumatism 58(11): 3319-3329.
CZP	28	Smolen, J., R. B. Landewe, et al. (2009). "Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial." Ann Rheum Dis 68(6): 797-804.
CZP	29	Fleischmann, R., et al., Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis, 2009. 68(6): p. 805-11.

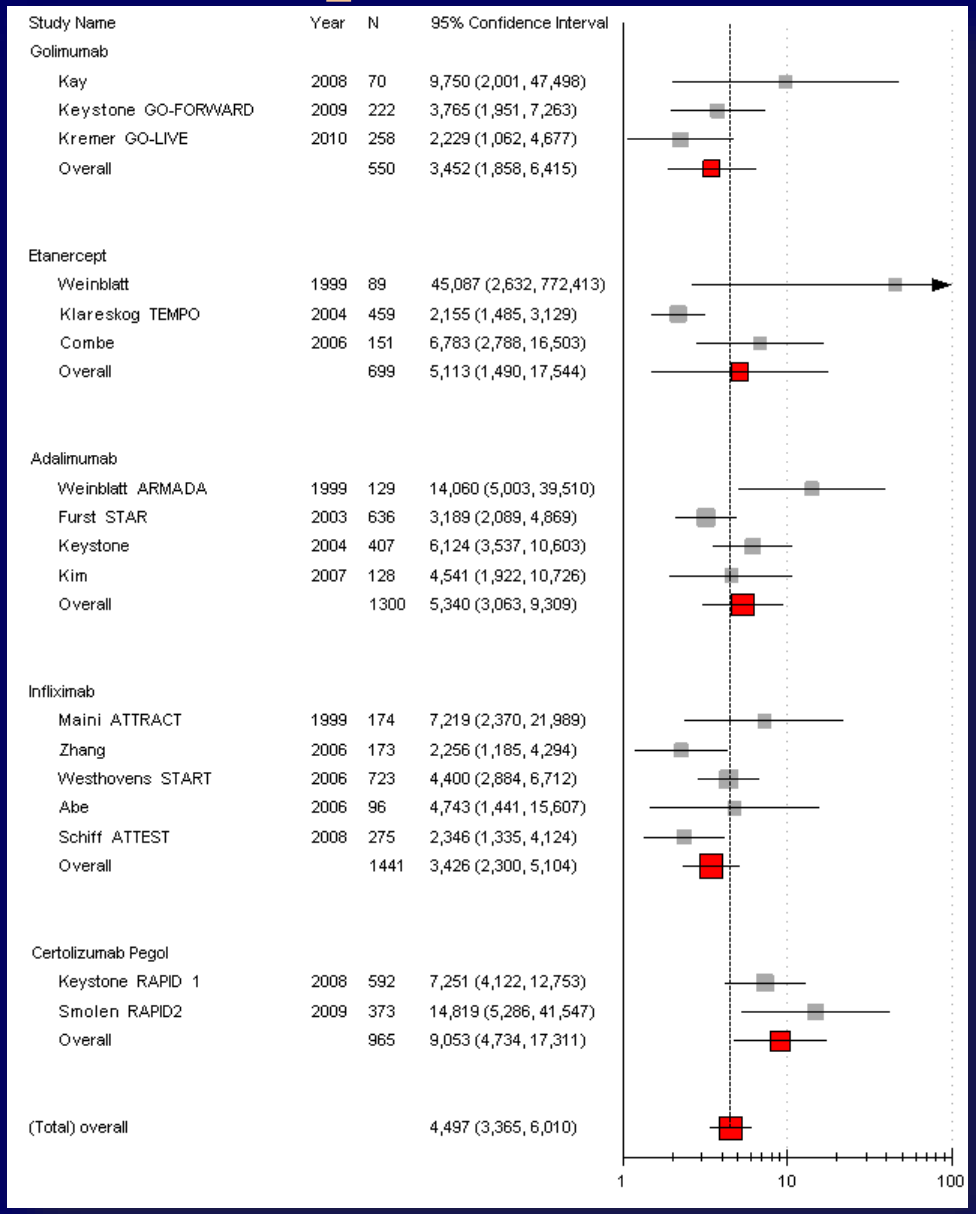
RCT Exclus

TTX	*N*	*Référence*	*Raison d'exclusion*
ETA	1	Bathon, J. M., R. W. Martin, et al. (2000). "A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis." New England Journal of Medicine 343(22): 1586-1593.	MTX naïf
ETA	2	Emery, P., F. C. Breedveld, et al. (2008). "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 372(9636): 375-382.	MTX naïf
ETA	3	Emery, P., F. Breedveld, et al. (2010). "Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritistwo-year, double-blind, randomized study." Arthritis Rheum 62(3): 674-682.	Essai séquentiel
ETA	4	Furst, D. E., N. Gaylis, et al. (2007). "Open-label, pilot protocol of patients with rheumatoid arthritis who switch to infliximab after an incomplete response to etanercept: the opposite study." Ann Rheum Dis 66(7): 893-899.	Open-label et ayant été traités avec ETA
ETA	5	Genovese, M. C., J. M. Bathon, et al. (2002). "Etanercept versus methotrexate in patients with early rheumatoid arthritis: Two-year radiographic and clinical outcomes." Arthritis and Rheumatism 46(6): 1443-1450.	MTX naïf
ETA	6	Johnsen, A. K., M. H. Schiff, et al. (2006). "Comparison of 2 doses of etanercept (50 vs 100 mg) in active rheumatoid arthritis: a randomized double blind study." J Rheumatol 33(4): 659-664.	Comparateur Etanercept 100
ETA	7	Keystone, E. C., M. H. Schiff, et al. (2004). "Once-Weekly Administration of 50 mg Etanercept in Patients with Active Rheumatoid Arthritis: Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial." Arthritis and Rheumatism 50(2): 353-363.	Essai séquenciel
ETA	8	Lan, J. L., S. J. Chou, et al. (2004). "A comparative study of etanercept plus methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis: A 12-week, double-blind, randomized, placebo-controlled study." Journal of the Formosan Medical Association 103(8): 618-623.	12 semaines
ETA	9	Moreland LW, Baumgartner SW, Schiff MH, Tindall EA, Fleischmann RM, Weaver AL, et al. "Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor" (p75)-Fc fusion protein. N Engl J Med 1997;337:141–7.	Essais à 3 mois
ETA	10	Van der Heijde, D., L. Klareskog, et al. (2007). "Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis." Arthritis Rheum 56(12): 3928-3939.	3ème année (déjà publié 1ère et 2ème années)
ETA	11	Weinblatt, M., M. Schiff, et al. (2007). "Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial." Ann Rheum Dis 66(2): 228-234.	Comparateur Abatacept
ETA	12	Weinblatt, M. E., M. H. Schiff, et al. (2008). "Efficacy and safety of etanercept 50 mg twice a week in patients with rheumatoid arthritis who had a suboptimal response to etanercept 50 mg once a week: results of a multicenter, randomized, double-blind, active drug-controlled study." Arthritis Rheum 58(7): 1921-1930.	12 semaines
ETA	13	Weisman, M. H., H. E. Paulus, et al. (2007). "A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases." Rheumatology (Oxford) 46(7): 1122-1125.	51,5% des patients naifs au MTX; Essai sur les comorbidités
ADA	14	Bejarano, V., M. Quinn, et al. (2008). "Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis." Arthritis Rheum 59(10): 1467-1474.	MTX naïf
ADA	15	Breedveld, F. C., M. H. Weisman, et al. (2006). "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 54(1): 26-37.	MTX naïf
ADA	16	Chen, D. Y., S. J. Chou, et al. (2009). "Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis." J Formos Med Assoc 108(4): 310-319.	12 semaines

RCT Exclus

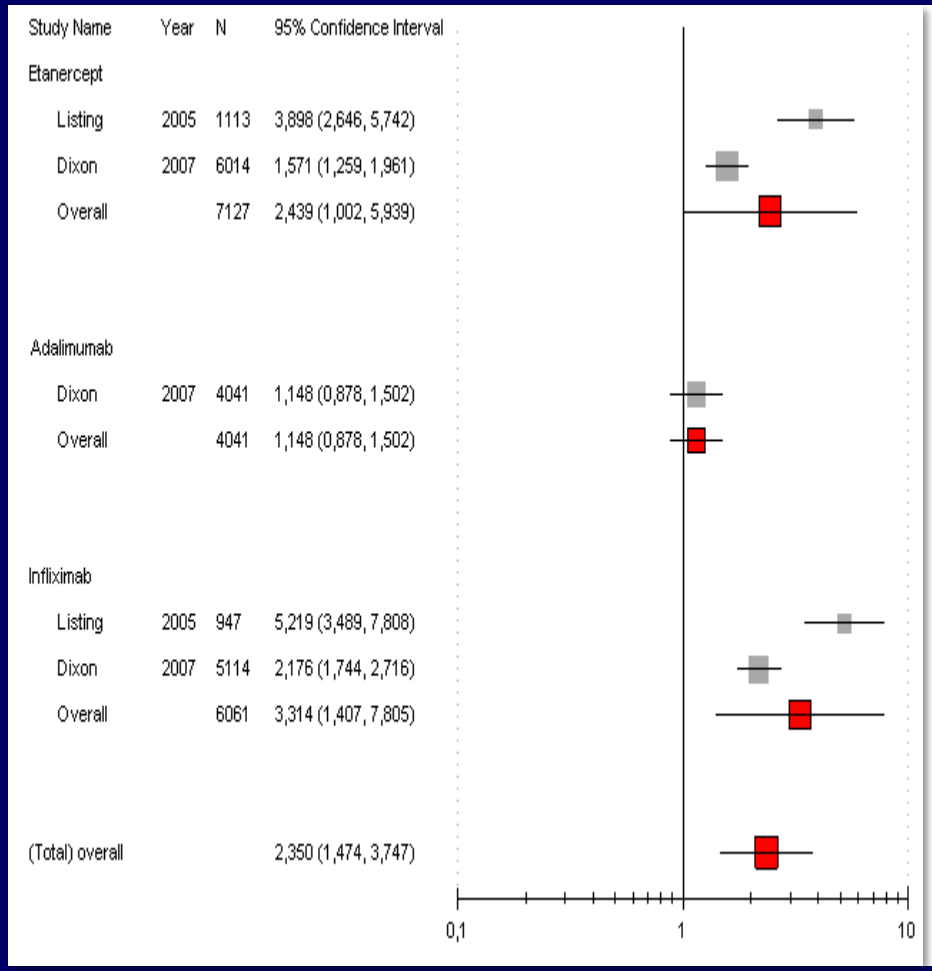
TTX	*N*	*Référence*	*Raison d'exclusion*
INF	17	Abe, T., T. Takeuchi, et al. (2006). "A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis." J Rheumatol 33(1): 37-44.	14 semaines
INF	18	Allaart, C. F., Y. P. Goekoop-Ruiterman, et al. (2006). "Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the best study." Clin Exp Rheumatol 24(6 Suppl 43): S-77-82.	Essai séquentiel
INF	19	Goekoop-Ruiterman, Y. P., J. K. De Vries-Bouwstra, et al. (2005). "Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the best study): a randomized, controlled trial." Arthritis Rheum 52(11): 3381-3390.	Essai séquentiel
INF	20	Pavelka, K., K. Jarosova, et al. (2009). "Increasing the infliximab dose in rheumatoid arthritis patients: a randomised, double blind study failed to confirm its efficacy." Ann Rheum Dis 68(8): 1285-1289.	Comparateur doses Infliximab
INF	21	Van Vollenhoven, R. F., S. Ernestam, et al. (2009). "Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial." Lancet 374(9688): 459-466.	40 semaines
INF	22	Westhovens R, Wolfe F, Rahman MU, et al. The safety and efficacy of infliximab therapy in RA. Poster presented at: European League Against Rheumatism Annual Scientific Meeting; June 9-12, 2004; Berlin, Germany.	Même article que 2006
GOL	23	Emery, P., R. M. Fleischmann, et al. (2009). "Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis." Arthritis Rheum 60(8): 2272-2283.	MTX naïf
GOL	24	Hall, S., J. Smolen, et al. (2009). "Golimumab, a human TNF-alpha monoclonal antibody, in rheumatoid arthritis patients previously treated with anti-TNF-A agents (go-after study)." Internal Medicine Journal 39(Full record): A71.	Même étude : Smolen
GOL	25	Nash, P., P. Emery, et al. (2009). "Golumumab, a new human anti-TNF-alpha monoclonal antibody, in methotrexate-naive active rheumatoid arthritis (go-before study)." Internal Medicine Journal 39(Full record): A71.	MTX naïf
GOL	26	Smolen, J. S., J. Kay, et al. (2009). "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 374(9685): 210-221.	Après d'échec d'un anti TNF
TCZ	27	Emery, P., E. Keystone, et al. (2008). "IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial." Ann Rheum Dis 67(11): 1516-1523.	Après d'échec d'un anti TNF
TCZ	28	Jones, G., A. Sebba, et al. (2010). "Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study." Ann Rheum Dis 69(1): 88-96.	2/3 des patients sont naifs au MTX

MA Classique ACR 50 RTC

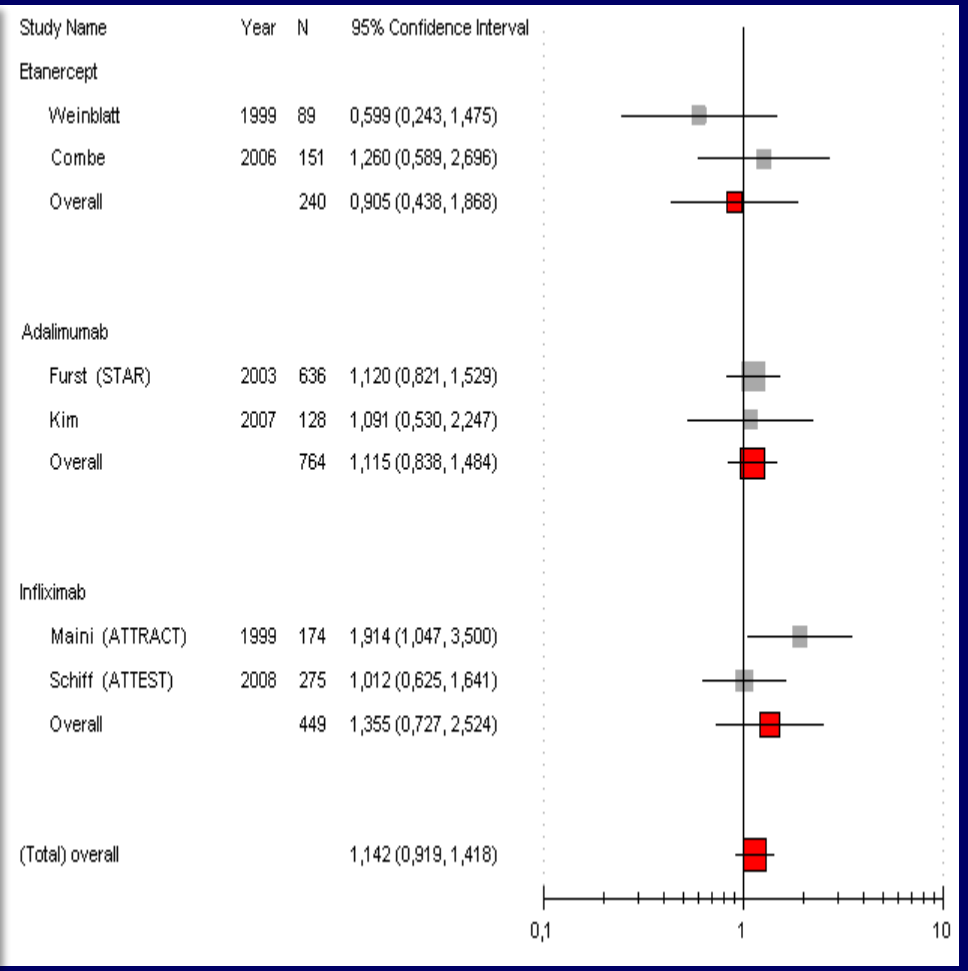


MA Classique Infections

Etudes observationelles

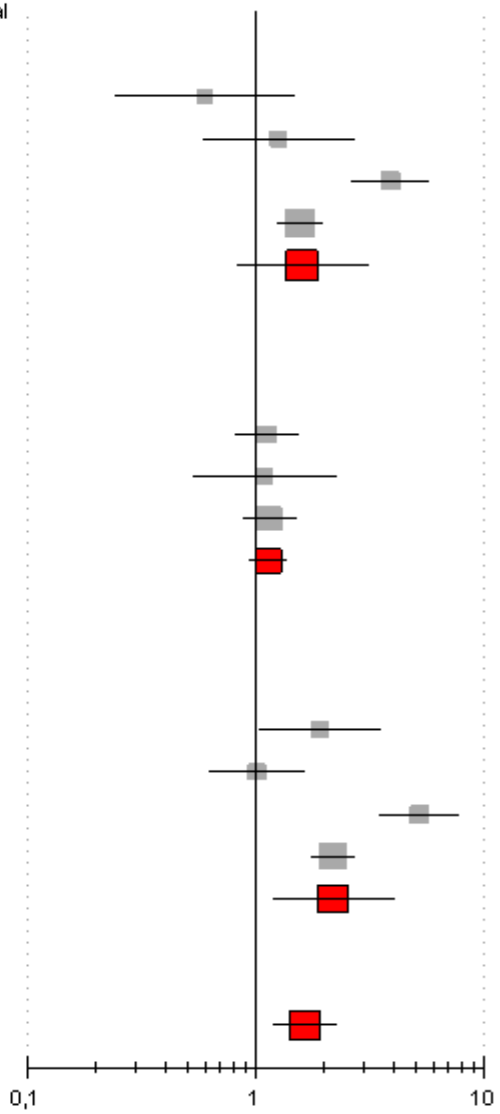


Essais Randomisés

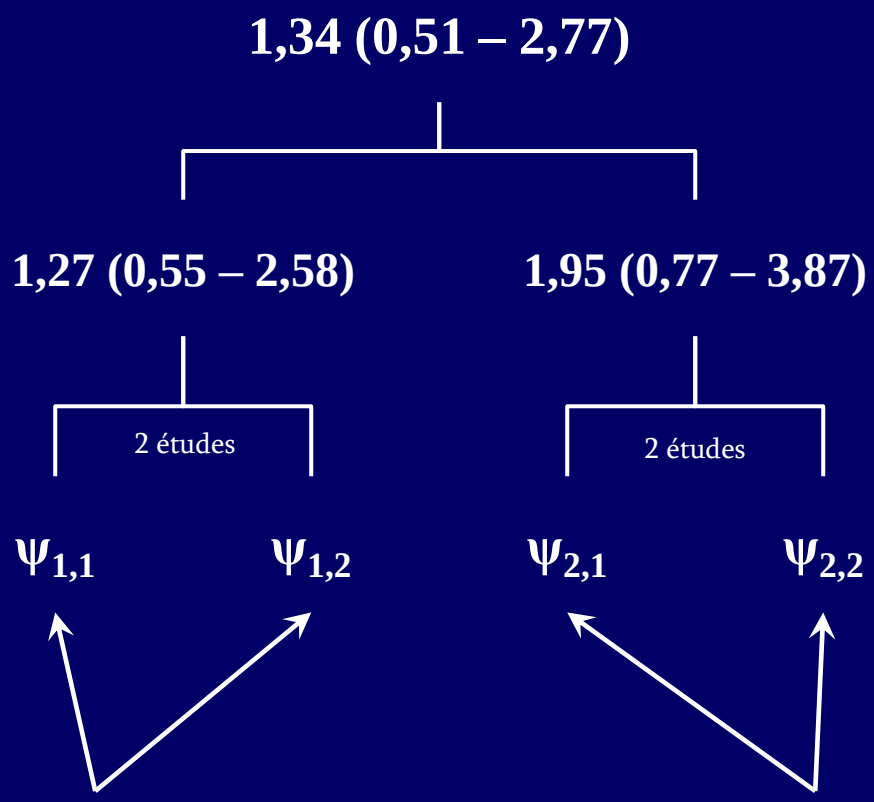


Meta Classique Effet Commun Infections

Study Name	Type étude	N	95% Confidence Interval
Etanercept			
Weinblatt	RCT	89	0,599 (0,243, 1,475)
Combe	RCT	151	1,260 (0,589, 2,696)
Lisitng	OBS	1113	3,898 (2,646, 5,742)
Dixon	OBS	6014	1,571 (1,259, 1,961)
Overall		7367	1,598 (0,826, 3,091)
Adalimumab			
Furst (STAR)	RCT	636	1,120 (0,821, 1,529)
Kim	RCT	128	1,091 (0,530, 2,247)
Dixon	OBS	4041	1,148 (0,878, 1,502)
Overall		4805	1,133 (0,931, 1,377)
Infliximab			
Maini (ATTRACT)	RCT	174	1,914 (1,047, 3,500)
Schiff (ATTEST)	RCT	275	1,012 (0,625, 1,641)
Listing	OBS	947	5,219 (3,489, 7,808)
Dixon	OBS	5114	2,176 (1,744, 2,716)
Overall		6510	2,195 (1,197, 4,022)
(Total) overall			1,649 (1,193, 2,281)



MA Hiérarchique Bayesienne: Infections Etanercept



Effet commun d'Etanercept estimé dans la population

Effet commun d'Etanercept estimé par type d'étude

Effet d'Etanercept estimé dans chaque étude

	Infections	
RCT	DMARD	Etanercept
Combe 2006	13/50	31/101
Weinblatt 1999	19/30	30/59

	Infections	
OBS	DMARD	Etanercept
Listing 2005	39/601	109/512
Dixon 2007	114/2170	308/3844

CONCLUSION

Selection Bibliographique

- Abrams K, Minelli C, Cooper N, Sutton A, Generalized evidence synthesis, CHEBS Seminar, November 2003
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- Smith TC, Abrams KR, Jones DR, Assessment of prior distributions and model parametrisation in hierarchical models for the generalized synthesis of evidence, University of Leicester, Technical Report 96-01
- Sutton AJ, Abrams KR, Jones DR, Prevost TC, Meta-analysis establishing treatment effect sizes: which data should be included and how far can results be extrapolated ?, University of Leicester 1999