

Poussée sévère corticorésistante de RCH : cyclosporine ou infliximab ?

Revue systématique et méta-analyse

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Cinquième Rencontre autour des MICI
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RCH sévère : Définition

Table 1.3 Disease activity in ulcerative colitis, adapted from Truelove and Witts'

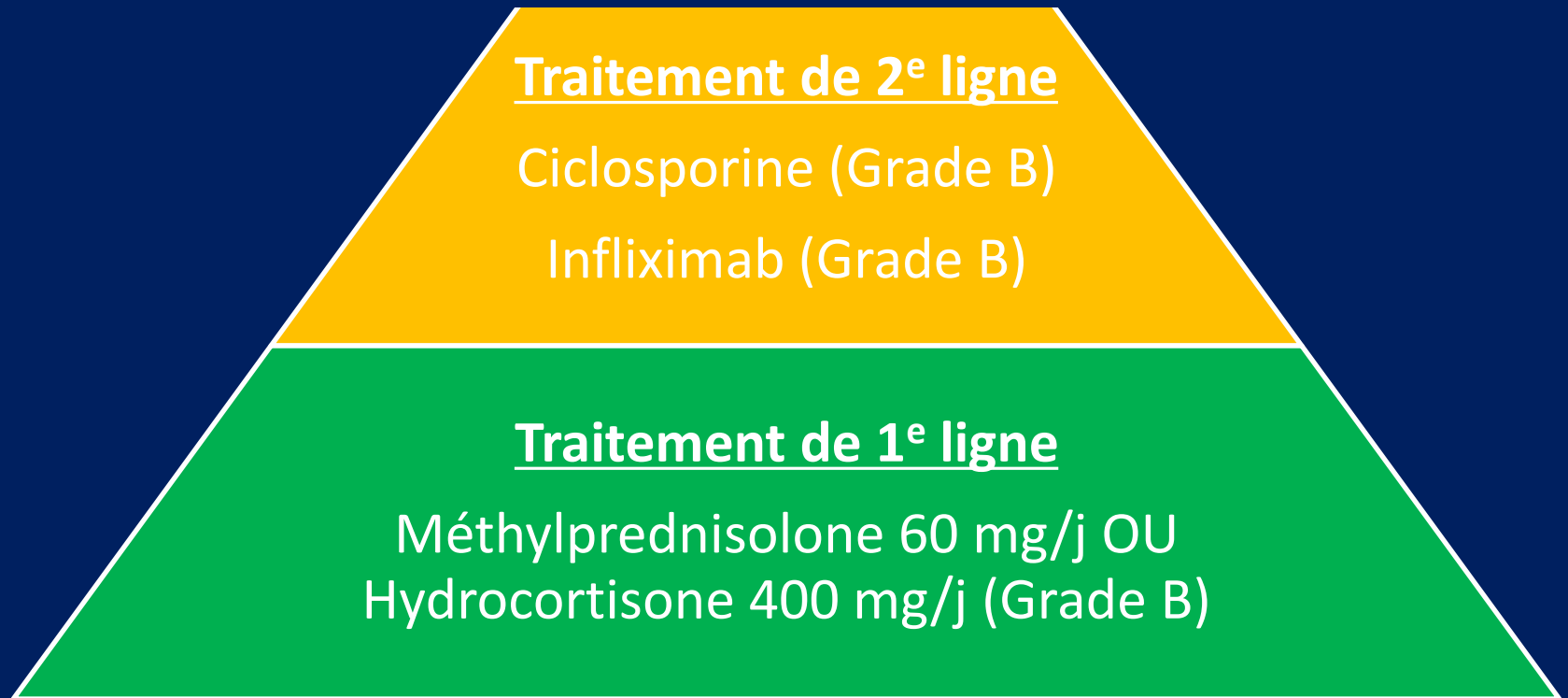
	Mild	Moderate 'in between mild and severe'	Severe
Bloody stools/day	<4	4 or more <i>if</i>	≥ 6 <i>and</i>
Pulse	<90 bpm	≤ 90 bpm	>90 bpm <i>or</i>
Temperature	<37.5 °C	≤ 37.8 °C	>37.8 °C <i>or</i>
Haemoglobin	>11.5 g/dL	≥ 10.5 g/dL	<10.5 g/dL <i>or</i>
ESR	<20 mm/h	≤ 30 mm/h	>30 mm/h <i>or</i>
or CRP	Normal	≤ 30 mg/L	>30 mg/L

Recommandations ECCO, 2008

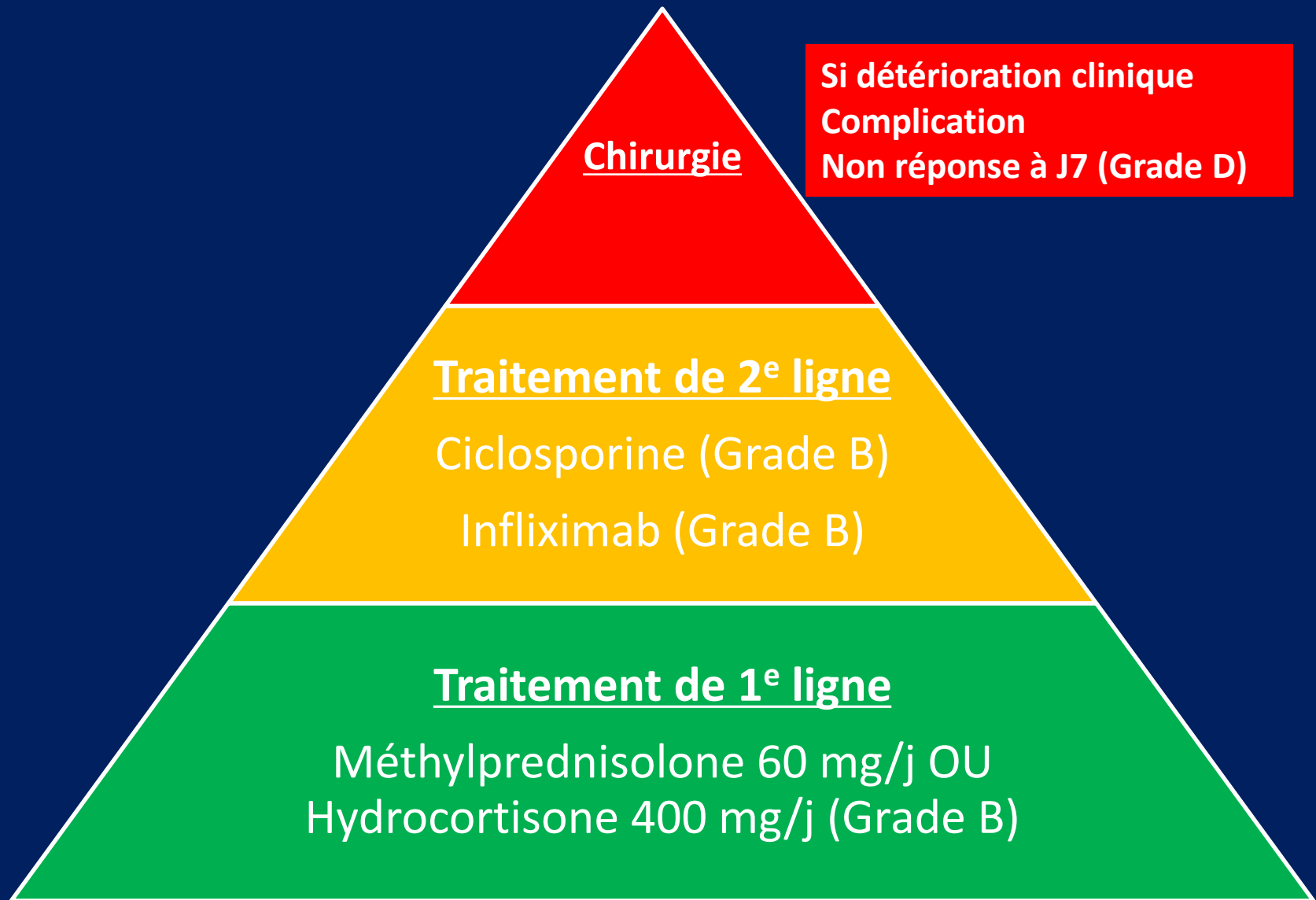
Traitement de 1^e ligne

Méthylprednisolone 60 mg/j OU
Hydrocortisone 400 mg/j (Grade B)

Recommandations ECCO, 2008



Recommandations ECCO, 2008



Cyclosporine, Infliximab
Quelle sont les évidences ?

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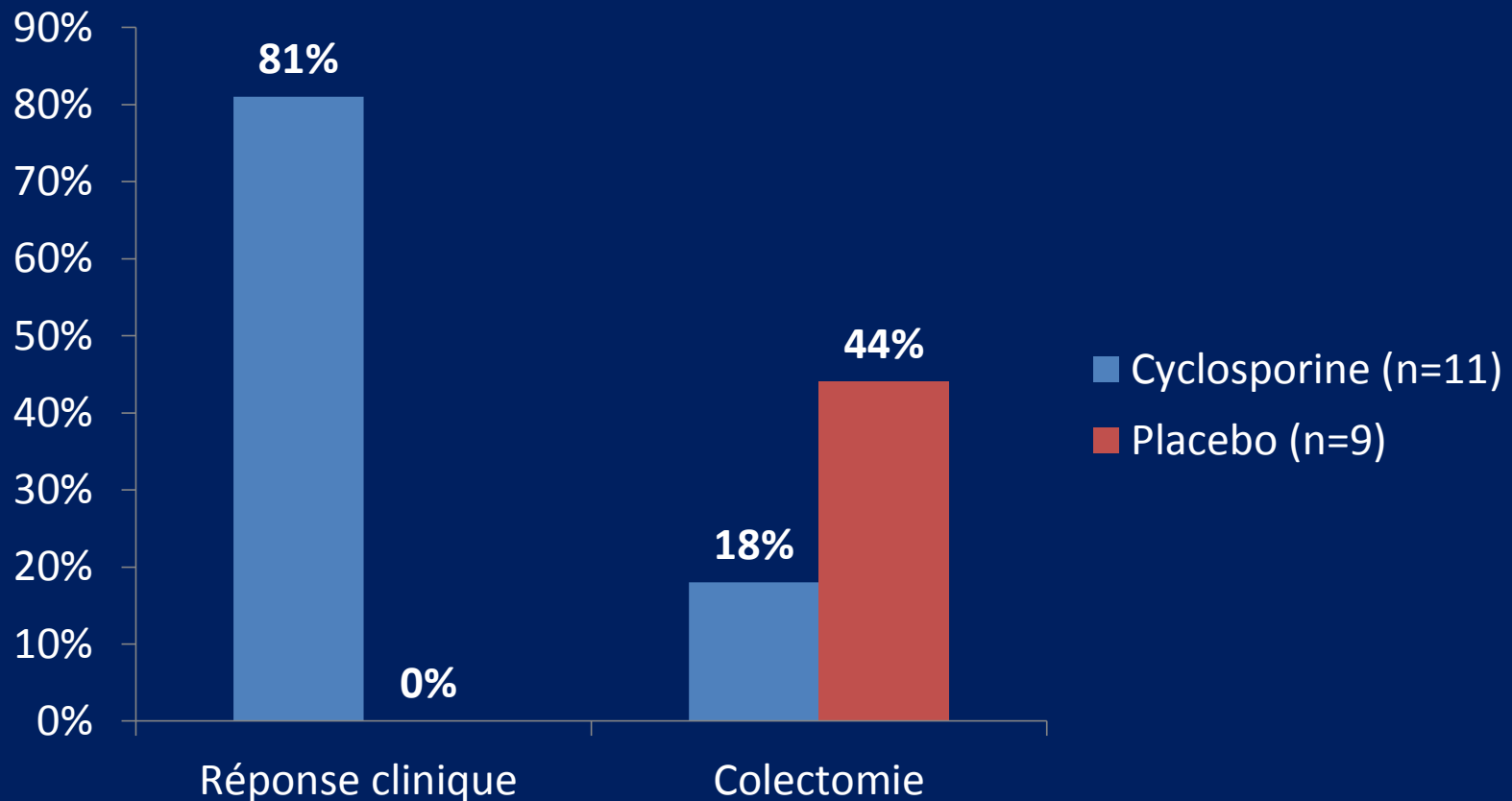
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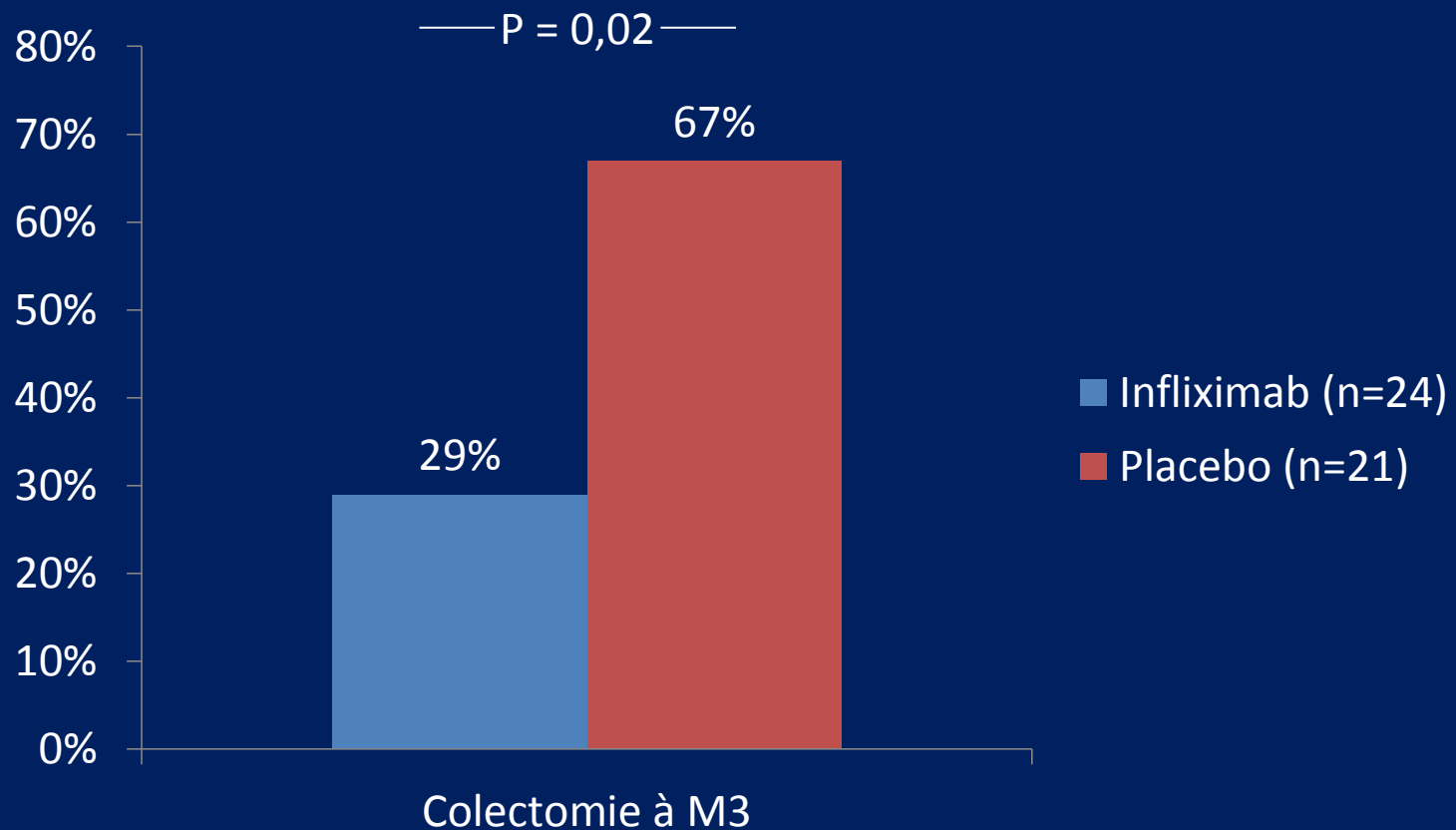
CYCLOSPORINE IN SEVERE ULCERATIVE COLITIS REFRACTORY TO STEROID THERAPY

SIMON LICHTIGER, M.D., DANIEL H. PRESENT, M.D., ASHER KORNBLUTH, M.D., IRWIN GELERNT, M.D.,
JOEL BAUER, M.D., GREG GALLER, M.D., FABRIZIO MICHELASSI, M.D., AND STEPHEN HANAUER, M.D.



Infliximab as Rescue Therapy in Severe to Moderately Severe Ulcerative Colitis: A Randomized, Placebo-Controlled Study

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CHRISTER GRÄNNÖ,# MOGENS VILIEN,** MAGNUS STRÖM,†† ÅKE DANIELSSON,§§
HANS VERBAAN,||| PER M. HELLSTRÖM,|| ANDERS MAGNUSON,¶¶ and BENGT CURMAN*



- Aucune comparaison directe des deux molécules ...

OBJECTIFS

- Revue systématique avec méta-analyse
- Efficacité de la cyclosporine et de l'infliximab
- RCH sévère cortico-résistante

METHODOLOGIE

Stratégie de recherche

- MEDLINE database (U.S. National Library of Medicine, Bethesda, MD, USA)
- European Crohn's and Colitis Organisation (2007 – 2010 incluse)
- American Digestive Disease Week (2007 – 2010 incluse)
- United European Gastroenterology Week (2006 – 2009 incluse)
- Mots-clés : ("colitis, ulcerative"[MeSH Terms] OR ("colitis"[All Fields] AND "ulcerative"[All Fields]) OR "ulcerative colitis"[All Fields] OR ("colitis"[All Fields] AND "ulcerative"[All Fields]) OR "colitis, ulcerative"[All Fields]) AND (("infliximab"[Substance Name] OR "infliximab"[All Fields]) OR ("cyclosporine"[MeSH Terms] OR "cyclosporine"[All Fields]))

Mesures étudiées

- **Réponse à court terme**

- Réponse clinique ou rémission au cours de l'hospitalisation ayant permis l'initiation de la cyclosporine ou de l'infliximab

- **Colectomie à court terme**

- Colectomie au cours de la même hospitalisation ayant permis l'administration de la cyclosporine ou de l'infliximab ou
- dans les 90 jours suivant le début du traitement.

- **Colectomie à long terme**

- Colectomie survenant au-delà du 90^e jour suivant le début du traitement par cyclosporine ou infliximab.

Analyse statistique

- Meta-analyse selon la méthode de Der-Simonian and Laird (Random effects).
- Hétérogénéité : χ^2 -based Q statistic ; I^2 statistic.
- Biais de publication : Funnel plots ; test Fail-Safe N de Rosenthal.
- Meta-régression : relation entre la posologie de la cyclosporine et les taux de réponse et de colectomie à court terme.

RESULTATS

1931 citations



108 citations correspondant aux critères de la revue systématique



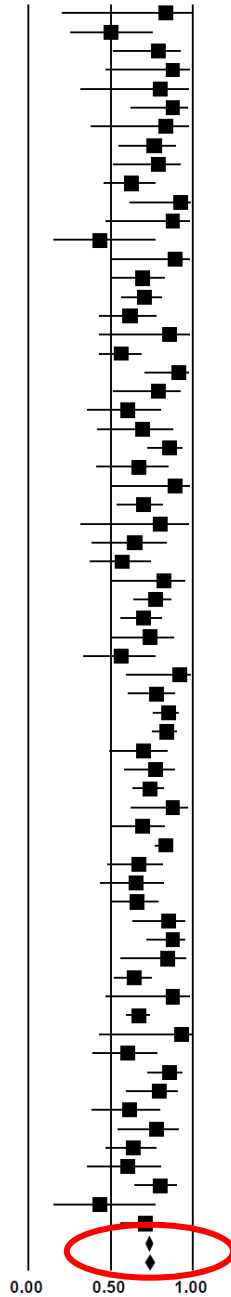
Exclusion
n = 13



95 études éligibles

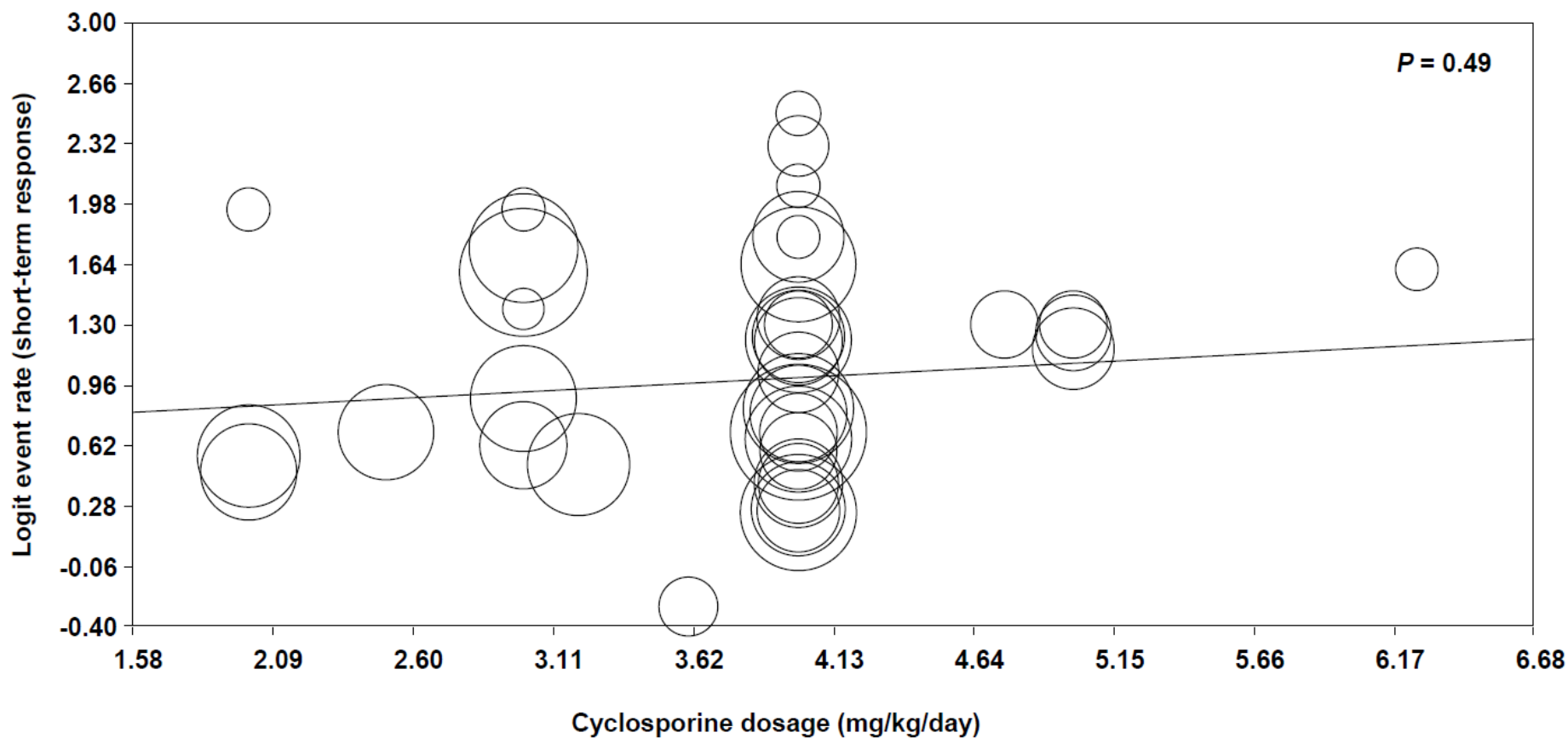
Réponse clinique à court terme

Model	Author	Year	Statistics for each study					Event rate and 95% CI
			Event rate	Lower limit	Upper limit	Z-Value	p-Value	
	Stange, E. F.	1989	0.833	0.194	0.990	1.039	0.299	
	Baker, K.	1989	0.500	0.244	0.756	0.000	1.000	
	Lichtiger, S.	1990	0.786	0.506	0.929	1.995	0.046	
	Actis, G. C.	1993	0.875	0.463	0.983	1.820	0.069	
	Benkov, K. J.	1994	0.800	0.309	0.973	1.240	0.215	
	Lichtiger, S.	1994	0.875	0.614	0.969	2.574	0.010	
	Wenzl, H.	1994	0.833	0.369	0.977	1.469	0.142	
	Santos, J.	1995	0.762	0.540	0.897	2.270	0.023	
	Treem, W. R.	1995	0.786	0.506	0.929	1.995	0.046	
	Carbonnel, F.	1996	0.625	0.449	0.773	1.399	0.162	
	Fernandez-Banares, F.	1996	0.923	0.609	0.989	2.387	0.017	
	Ramakrishna, J.	1996	0.875	0.463	0.983	1.820	0.069	
	Reimund, J. M.	1997	0.429	0.144	0.770	-0.377	0.706	
	Symon, Z.	1997	0.889	0.500	0.985	1.961	0.050	
	Van Gossum, A.	1997	0.690	0.503	0.830	1.989	0.047	
	Actis, G. C.	1998	0.702	0.558	0.815	2.688	0.007	
	Actis, G. C.	1998	0.615	0.421	0.779	1.166	0.244	
	Dejaco, C.	1998	0.857	0.419	0.980	1.659	0.097	
	Hyde, G. M.	1998	0.560	0.421	0.690	0.846	0.397	
	Stack, W. A.	1998	0.909	0.700	0.977	3.105	0.002	
	Wenzl, H.	1998	0.786	0.506	0.929	1.995	0.046	
	Actis, G. C.	1998	0.600	0.348	0.808	0.769	0.442	
	Taylor, A. C.	1998	0.692	0.409	0.880	1.349	0.177	
	Cohen, R. D.	1999	0.857	0.717	0.934	4.063	0.000	
	Hermida-Rodriguez, C.	1999	0.667	0.406	0.854	1.266	0.206	
	Actis, G. C.	1999	0.889	0.500	0.985	1.961	0.050	
	Rowe, F. A.	2000	0.694	0.528	0.822	2.269	0.023	
	Ortiz, V.	2000	0.800	0.309	0.973	1.240	0.215	
	D'Haens, G.	2001	0.643	0.376	0.843	1.054	0.292	
	Kjeldsen, J.	2001	0.565	0.363	0.748	0.624	0.533	
	Navazo, L.	2001	0.818	0.493	0.954	1.924	0.054	
	Domenech, E.	2002	0.771	0.632	0.868	3.532	0.000	
	McCormack, G.	2002	0.696	0.549	0.811	2.580	0.010	
	Rolny, P.	2002	0.737	0.502	0.886	1.976	0.048	
	Campbell, S.	2003	0.563	0.324	0.775	0.499	0.618	
	Okamura, S.	2003	0.917	0.587	0.988	2.296	0.022	
	Rayner, C. K.	2003	0.774	0.596	0.888	2.868	0.004	
	Van Assche, G.	2003	0.849	0.748	0.915	5.285	0.000	
	Arts, J.	2004	0.837	0.744	0.901	5.606	0.000	
	Actis, G. C.	2004	0.696	0.485	0.847	1.824	0.068	
	Message, L.	2005	0.769	0.572	0.892	2.587	0.010	
	Campbell, S.	2005	0.737	0.627	0.823	3.953	0.000	
	de Saussure, P.	2005	0.875	0.614	0.969	2.574	0.010	
	Cerezo Ruiz, A.	2006	0.690	0.503	0.830	1.989	0.047	
	Moskovitz, D. N.	2006	0.831	0.760	0.884	7.112	0.000	
	Reddy, Y.	2006	0.667	0.473	0.817	1.698	0.090	
	Singh, G.	2006	0.650	0.426	0.823	1.320	0.187	
	Thomas, T.	2006	0.658	0.496	0.790	1.912	0.056	
	Weber, A.	2006	0.850	0.624	0.951	2.770	0.006	
	Castro, M.	2007	0.875	0.711	0.952	3.640	0.000	
	Chermesh, I.	2007	0.846	0.549	0.961	2.218	0.027	
	Actis, G. C.	2007	0.639	0.512	0.749	2.147	0.032	
	Branche, J.	2008	0.875	0.463	0.983	1.820	0.069	
	Cacheux, W.	2008	0.667	0.583	0.741	3.797	0.000	
	Chandra, N.	2008	0.929	0.423	0.996	1.748	0.081	
	Huguet Malaves, J. M.	2008	0.600	0.380	0.786	0.888	0.374	
	Shah, S.B.	2008	0.857	0.717	0.934	4.063	0.000	
	Sood, A.	2008	0.792	0.587	0.911	2.656	0.008	
	Chandra, N.	2008	0.611	0.379	0.802	0.935	0.350	
	Holme, O.	2009	0.778	0.535	0.914	2.210	0.027	
	Mocciaro, F.	2009	0.636	0.463	0.781	1.546	0.122	
	Watanabe, O.	2009	0.600	0.348	0.808	0.769	0.442	
	Nieminen, U.	2009	0.800	0.636	0.902	3.281	0.001	
	Bossa, F.	2009	0.429	0.144	0.770	-0.377	0.706	
	Bamba, S.	2010	0.707	0.552	0.826	2.571	0.010	
Fixed effect			0.726	0.704	0.747	17.646	< 0.0001	
Random effects			0.730	0.702	0.757	14.036	< 0.0001	



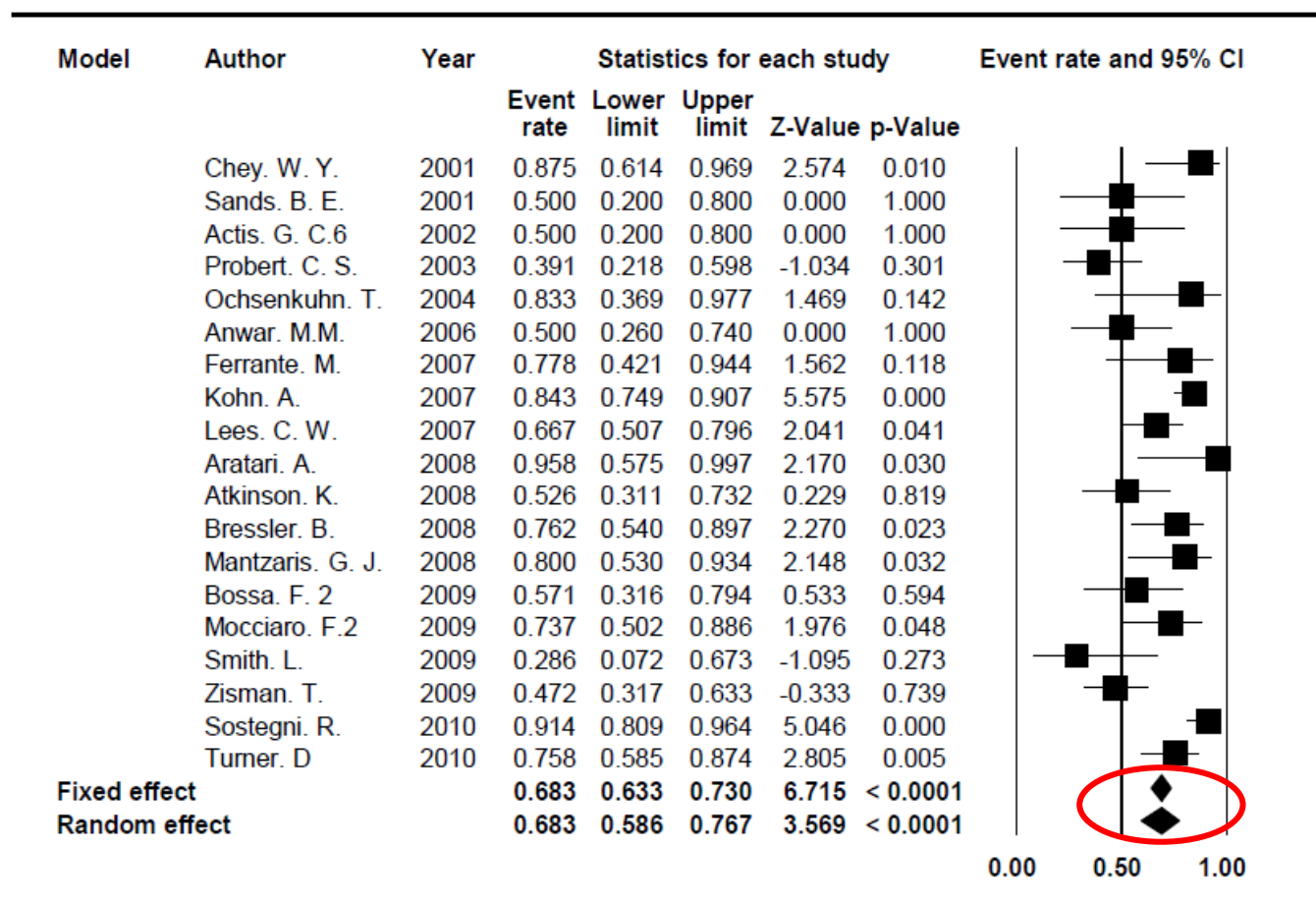
Cyclosporine

Réponse clinique à court terme :
73% (70,2% à 75,7%)

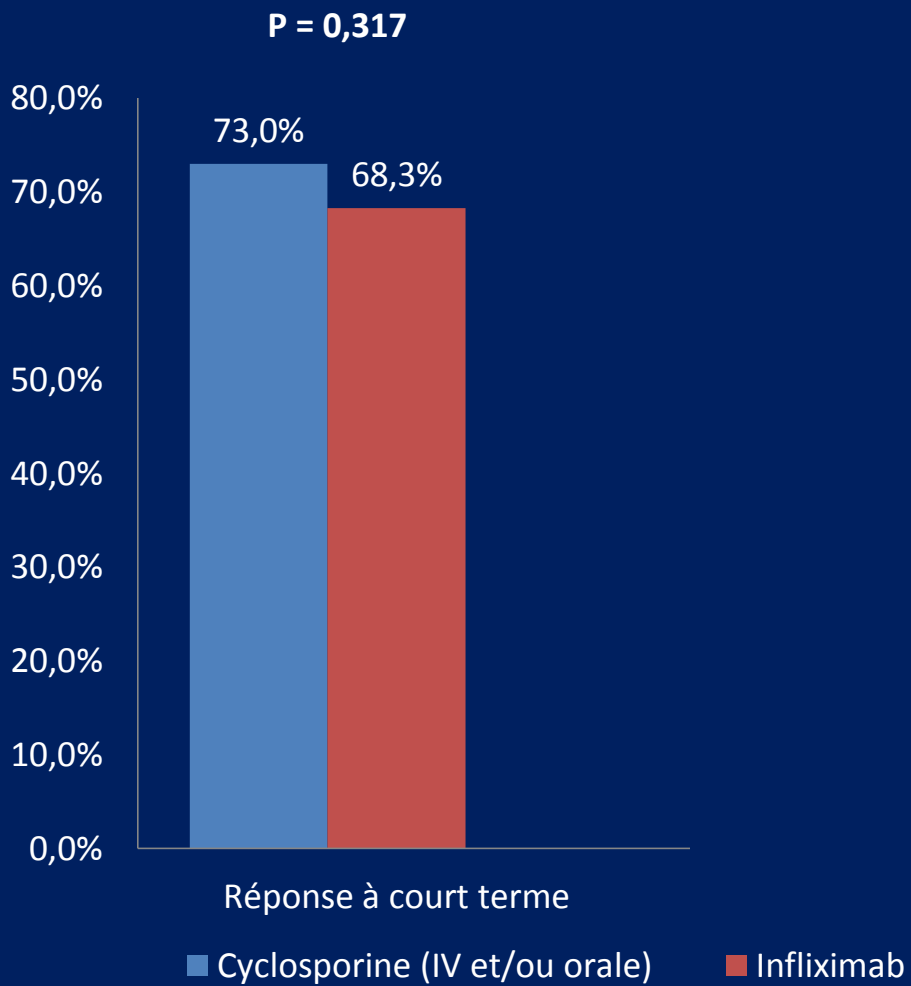


Réponse clinique à court terme en fonction de la posologie de la cyclosporine

Infliximab



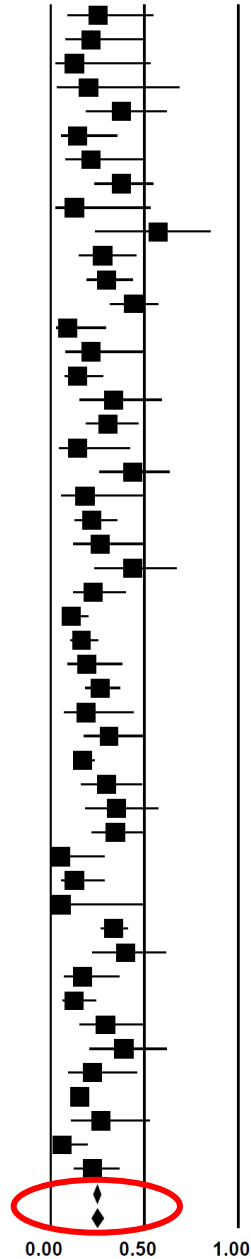
Réponse clinique à court terme :
68,3% (58,6% à 76,7%)



*Mixed effects analysis

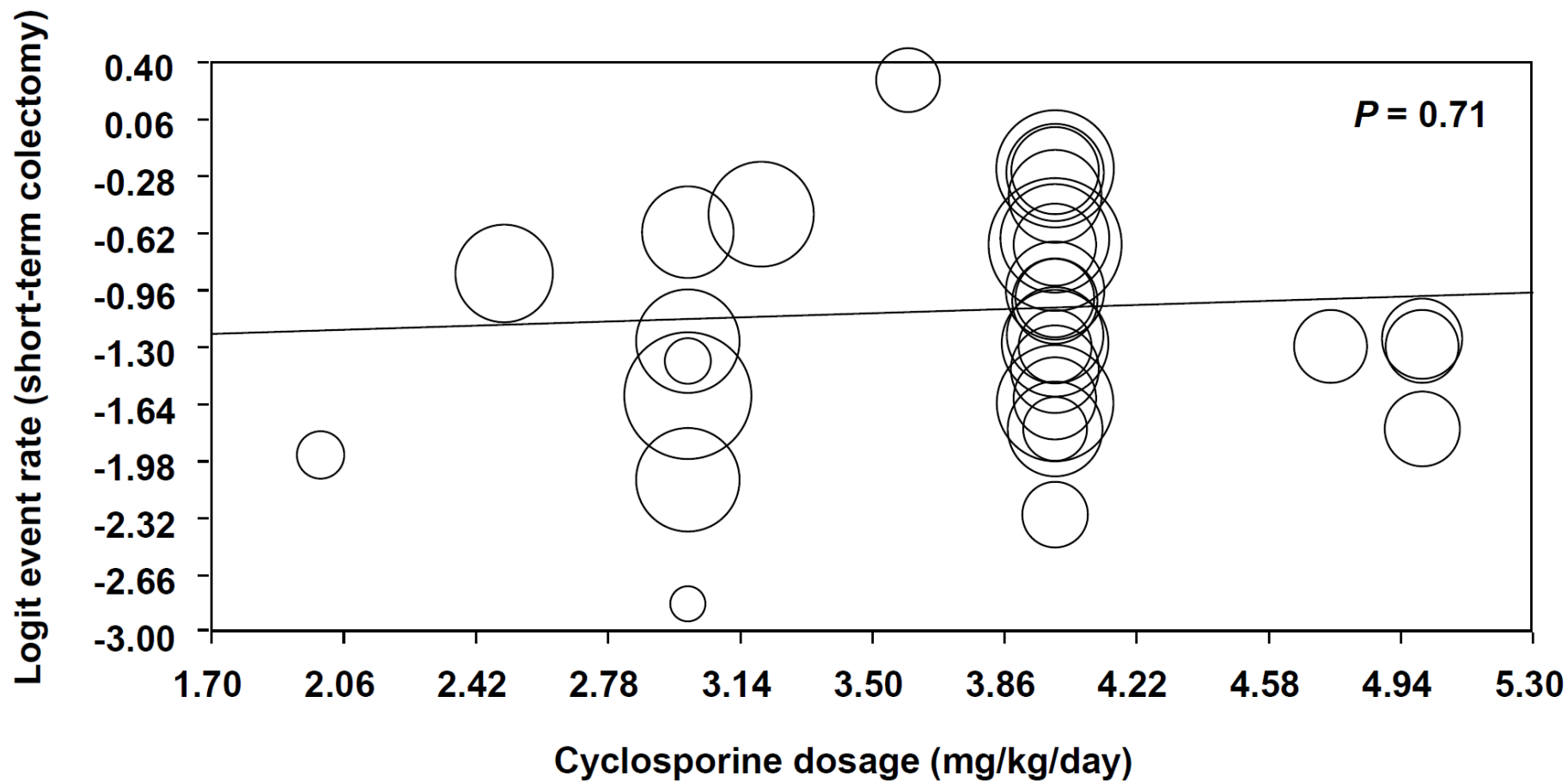
Colectomie à court terme

Model	Author	Year	Statistics for each study					Event rate and 95% CI
			Event rate	Lower limit	Upper limit	Z-Value	p-Value	
	Baker, K.	1989	0.250	0.083	0.552	-1.648	0.099	
	Lichtiger, S.	1990	0.214	0.071	0.494	-1.995	0.046	
	Actis, G. C.	1993	0.125	0.017	0.537	-1.820	0.069	
	Benkov, K. J.	1994	0.200	0.027	0.691	-1.240	0.215	
	Lichtiger, S.	1994	0.375	0.179	0.623	-0.989	0.323	
	Santos, J.	1995	0.143	0.047	0.361	-2.873	0.004	
	Treem, W. R.	1995	0.214	0.071	0.494	-1.995	0.046	
	Carbonnel, F.	1996	0.375	0.227	0.551	-1.399	0.162	
	Ramakrishna, J.	1996	0.125	0.017	0.537	-1.820	0.069	
	Reimund, J. M.	1997	0.571	0.230	0.856	0.377	0.706	
	Van Gossum, A.	1997	0.276	0.144	0.462	-2.323	0.020	
	Actis, G. C.	1998	0.298	0.185	0.442	-2.688	0.007	
	Hyde, G. M.	1998	0.440	0.310	0.579	-0.846	0.397	
	Stack, W. A.	1998	0.091	0.023	0.300	-3.105	0.002	
	Wenzl, H.	1998	0.214	0.071	0.494	-1.995	0.046	
	Cohen, R. D.	1999	0.143	0.066	0.283	-4.063	0.000	
	Hermida-Rodriguez, C.	1999	0.333	0.146	0.594	-1.266	0.206	
	Rowe, F. A.	2000	0.306	0.178	0.472	-2.269	0.023	
	D'Haens, G.	2001	0.143	0.036	0.427	-2.346	0.019	
	Kjeldsen, J.	2001	0.435	0.252	0.637	-0.624	0.533	
	Navazo, L.	2001	0.182	0.046	0.507	-1.924	0.054	
	McCormack, G.	2002	0.217	0.121	0.359	-3.583	0.000	
	Rolny, P.	2002	0.263	0.114	0.498	-1.976	0.048	
	Campbell, S.	2003	0.438	0.225	0.676	-0.499	0.618	
	Rayner, C. K.	2003	0.226	0.112	0.404	-2.868	0.004	
	Van Assche, G.	2003	0.110	0.056	0.204	-5.591	0.000	
	Arts, J.	2004	0.163	0.099	0.256	-5.606	0.000	
	Message, L.	2005	0.192	0.082	0.387	-2.884	0.004	
	Campbell, S.	2005	0.263	0.177	0.373	-3.953	0.000	
	de Saussure, P.	2005	0.188	0.062	0.447	-2.289	0.022	
	Cerezo Ruiz, A.	2006	0.310	0.170	0.497	-1.989	0.047	
	Moskovitz, D. N.	2006	0.169	0.116	0.240	-7.112	0.000	
	Reddy, Y.	2006	0.296	0.156	0.490	-2.052	0.040	
	Singh, G.	2006	0.350	0.177	0.574	-1.320	0.187	
	Thomas, T.	2006	0.342	0.210	0.504	-1.912	0.056	
	Weber, A.	2006	0.053	0.007	0.294	-2.813	0.005	
	Castro, M.	2007	0.125	0.048	0.289	-3.640	0.000	
	Branche, J.	2008	0.056	0.003	0.505	-1.947	0.052	
	Cacheux, W.	2008	0.333	0.259	0.417	-3.797	0.000	
	Huguet Malaves, J. M.	2008	0.400	0.214	0.620	-0.888	0.374	
	Sood, A.	2008	0.167	0.064	0.369	-2.938	0.003	
	Walch, A.	2008	0.122	0.056	0.247	-4.519	0.000	
	Chandra, N.	2008	0.292	0.146	0.498	-1.976	0.048	
	Chandra, N.	2008	0.389	0.198	0.621	-0.935	0.350	
	Holme, O.	2009	0.222	0.086	0.465	-2.210	0.027	
	Sauk, J.	2009	0.153	0.116	0.200	-10.430	0.000	
	Watanabe, O.	2009	0.267	0.104	0.533	-1.733	0.083	
	Nieminen, U.	2009	0.057	0.014	0.202	-3.850	0.000	
	Bamba, S.	2010	0.220	0.118	0.371	-3.362	0.001	
Fixed effect			0.240	0.220	0.262	-19.850	< 0.0001	
Random effect			0.241	0.211	0.275	-12.741	< 0.0001	



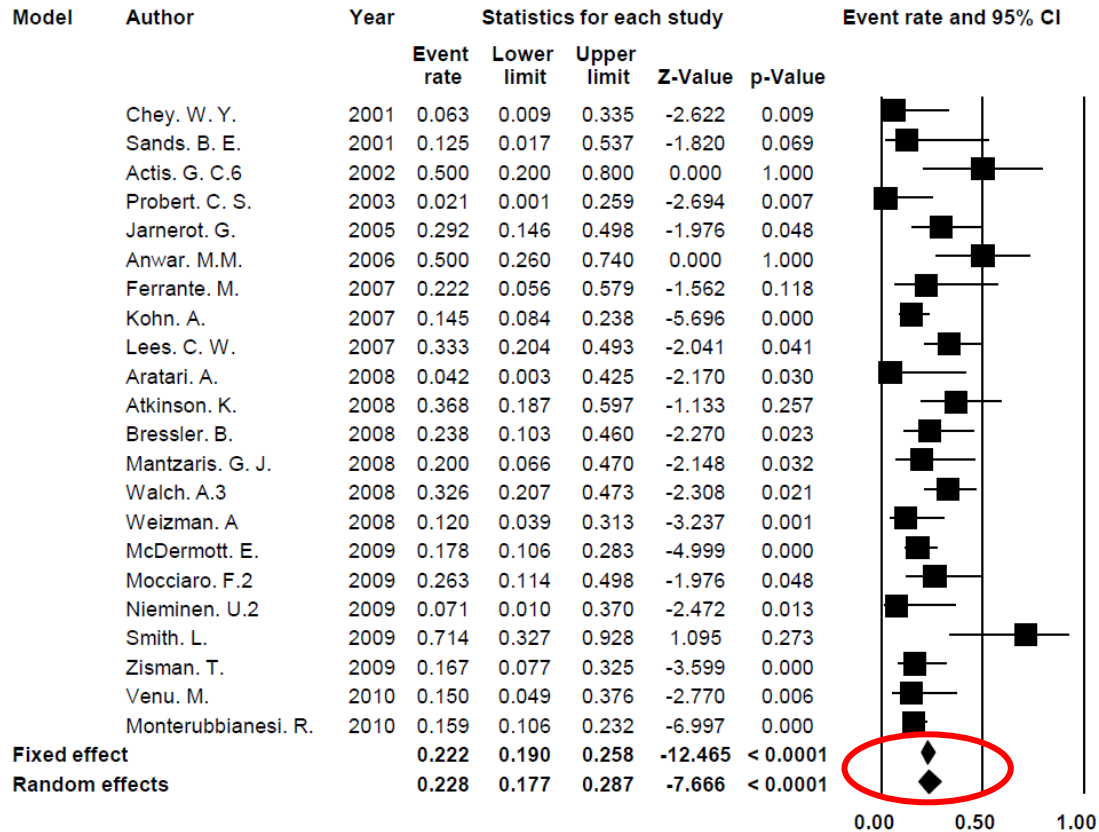
Cyclosporine

Colectomie à court terme :
24,1% (21,1% à 27,5%)

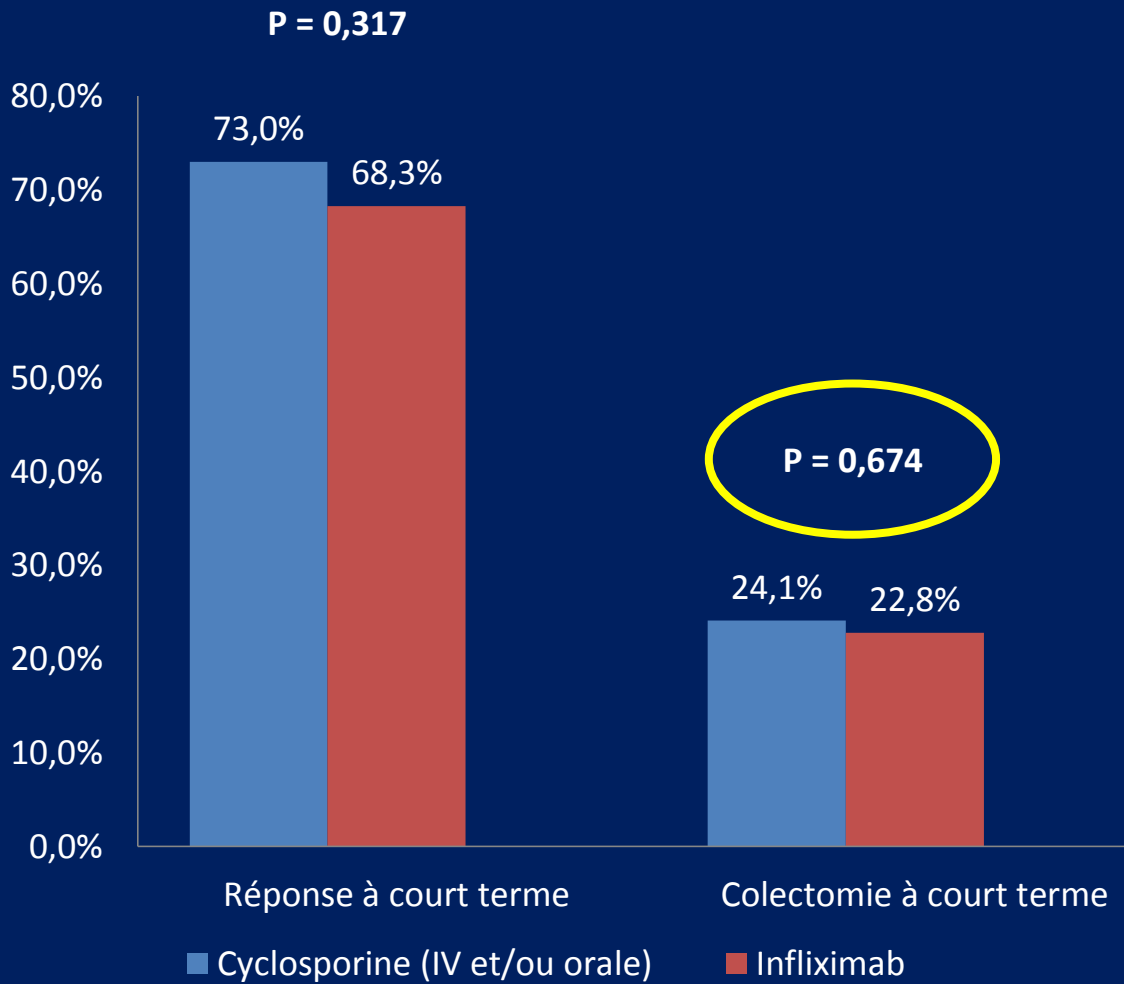


Colectomie à court terme en fonction de la posologie de la cyclosporine

Infliximab



Réponse clinique à court terme :
22,8% (17,7% à 28,7%)



*Mixed effects analysis

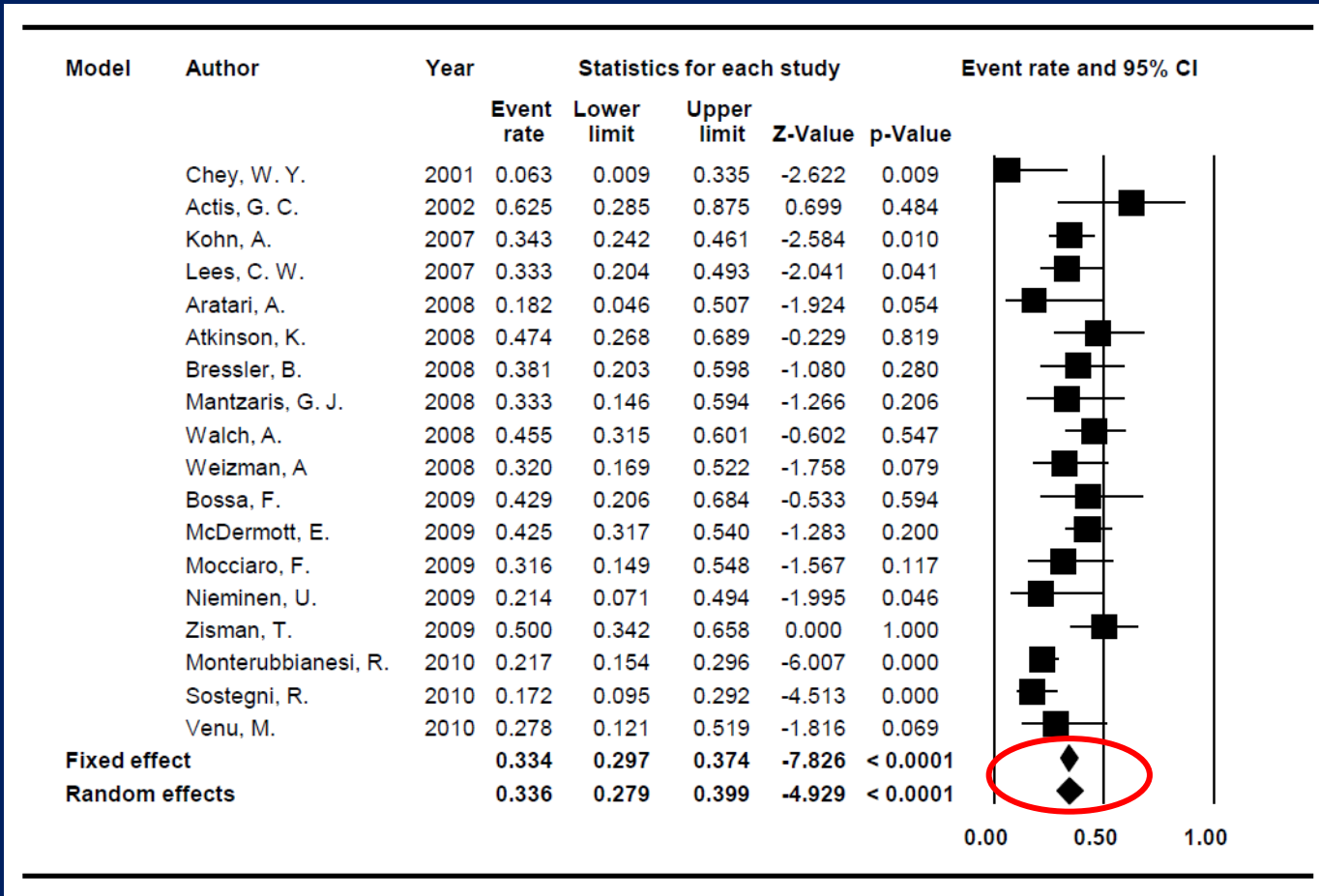
Colectomie à long terme

Model	Author	Year	Statistics for each study					Event rate and 95% CI
			Event rate	Lower limit	Upper limit	Z-Value	p-Value	
	Lichtiger. S.	1990	0.286	0.111	0.561	-1.549	0.121	
	Benkov. K. J.	1994	0.917	0.378	0.995	1.623	0.105	
	Lichtiger. S.	1994	0.438	0.225	0.676	-0.499	0.618	
	Santos. J.	1995	0.286	0.134	0.508	-1.897	0.058	
	Treem. W. R.	1995	0.714	0.439	0.889	1.549	0.121	
	Carbonnel. F.	1996	0.688	0.510	0.823	2.067	0.039	
	Ramakrishna. J.	1996	0.125	0.017	0.537	-1.820	0.069	
	Reimund. J. M.	1997	0.714	0.327	0.928	1.095	0.273	
	Van Gossum. A.	1997	0.517	0.341	0.689	0.186	0.853	
	Actis. G. C.	1998	0.383	0.256	0.528	-1.589	0.112	
	Hyde. G. M.	1998	0.600	0.460	0.725	1.405	0.160	
	Stack. W. A.	1998	0.455	0.265	0.659	-0.426	0.670	
	Wenzl. H.	1998	0.500	0.260	0.740	0.000	1.000	
	Cohen. R. D.	1999	0.381	0.248	0.534	-1.528	0.127	
	Hermida-Rodriguez. C.	1999	0.467	0.241	0.707	-0.258	0.796	
	Naftali. T.	2000	0.563	0.390	0.721	0.705	0.481	
	Rowe. F. A.	2000	0.667	0.500	0.800	1.961	0.050	
	D'Haens. G.	2001	0.357	0.157	0.624	-1.054	0.292	
	Kjeldsen. J.	2001	0.652	0.443	0.816	1.436	0.151	
	Navazo. L.	2001	0.455	0.203	0.732	-0.301	0.763	
	Domenech. E.	2002	0.289	0.168	0.451	-2.510	0.012	
	McCormack. G.	2002	0.587	0.441	0.719	1.173	0.241	
	Rolny. P.	2002	0.316	0.149	0.548	-1.567	0.117	
	Campbell. S.	2003	0.438	0.225	0.676	-0.499	0.618	
	Okamura. S.	2003	0.250	0.083	0.552	-1.648	0.099	
	Rayner. C. K.	2003	0.548	0.374	0.711	0.538	0.591	
	Arts. J.	2004	0.372	0.277	0.479	-2.345	0.019	
	Actis. G. C.	2004	0.217	0.093	0.428	-2.534	0.011	
	Message. L.	2005	0.462	0.284	0.650	-0.392	0.695	
	Campbell. S.	2005	0.579	0.466	0.684	1.371	0.170	
	Cerezo Ruiz. A.	2006	0.379	0.224	0.564	-1.287	0.198	
	Moskovitz. D. N.	2006	0.458	0.378	0.540	-1.006	0.315	
	Reddy. Y.	2006	0.333	0.183	0.527	-1.698	0.090	
	Singh. G.	2006	0.750	0.522	0.892	2.127	0.033	
	Weber. A.	2006	0.263	0.114	0.498	-1.976	0.048	
	Castro. M.	2007	0.281	0.153	0.458	-2.386	0.017	
	Branche. J.	2008	0.250	0.063	0.623	-1.346	0.178	
	Cacheux. W.	2008	0.556	0.471	0.637	1.288	0.198	
	Cheifetz.A.S.	2008	0.702	0.558	0.815	2.688	0.007	
	Huguet Malaves. J. M.	2008	0.600	0.380	0.786	0.888	0.374	
	Shah. S.B.	2008	0.548	0.397	0.690	0.616	0.538	
	Sood. A.	2008	0.333	0.176	0.539	-1.601	0.109	
	Walch. A.	2008	0.265	0.161	0.405	-3.148	0.002	
	Holme. O.	2009	0.556	0.330	0.760	0.470	0.638	
	Mocciaro. F.	2009	0.429	0.240	0.640	-0.652	0.514	
	Watanabe. O.	2009	0.667	0.406	0.854	1.266	0.206	
	Nieminen. U.	2009	0.171	0.079	0.333	-3.513	0.000	
	Bossa. F.	2009	0.429	0.144	0.770	-0.377	0.706	
	Bamba. S.	2010	0.293	0.174	0.448	-2.571	0.010	
	Walch. A.	2010	0.297	0.198	0.419	-3.151	0.002	
Fixed effect			0.462	0.437	0.488	-2.894	0.004	
Random effects			0.452	0.408	0.497	-2.109	0.035	

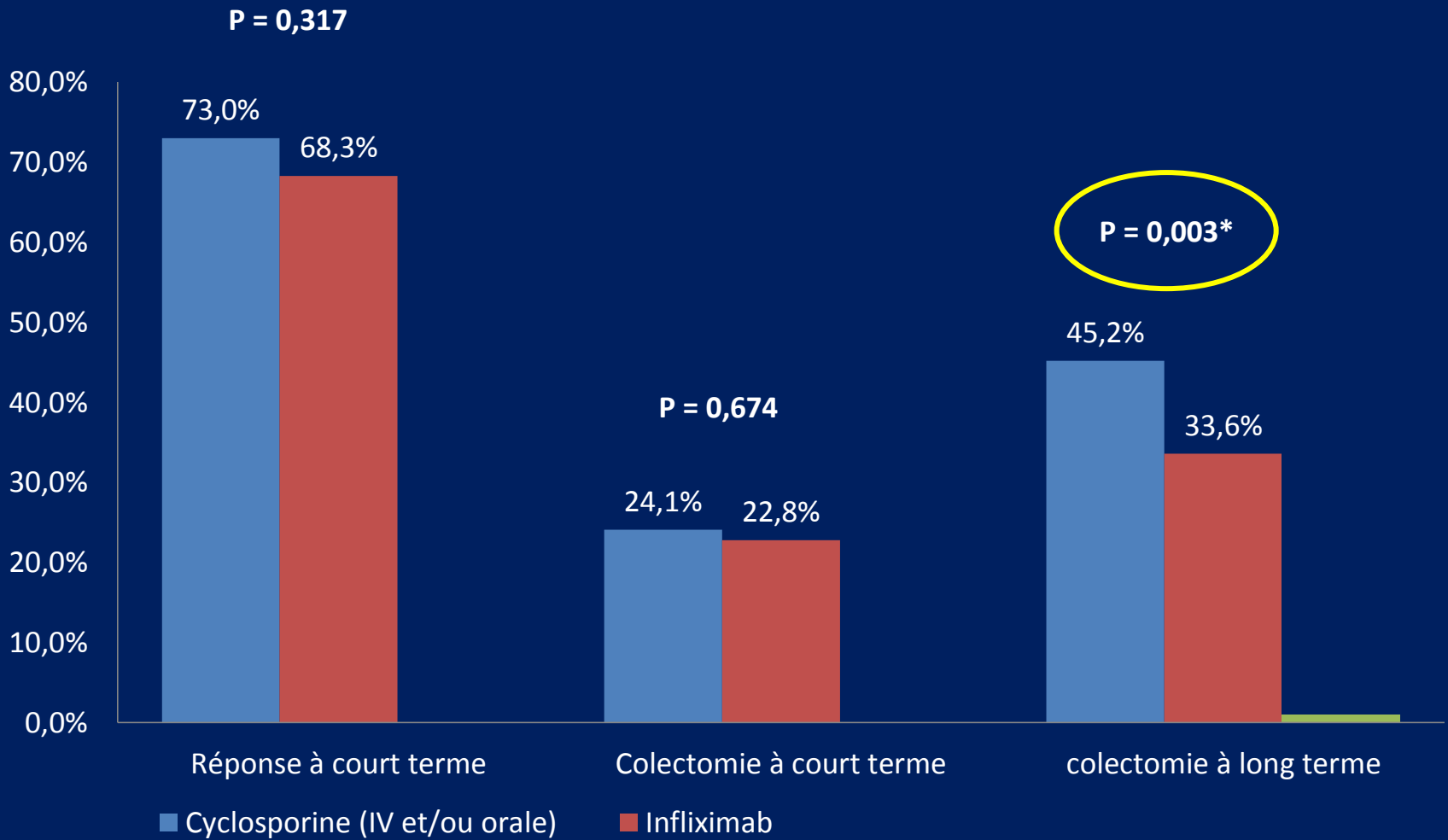
Cyclosporine

Colectomie à long terme :
45,2% (40,8% à 49,7%)

Infliximab



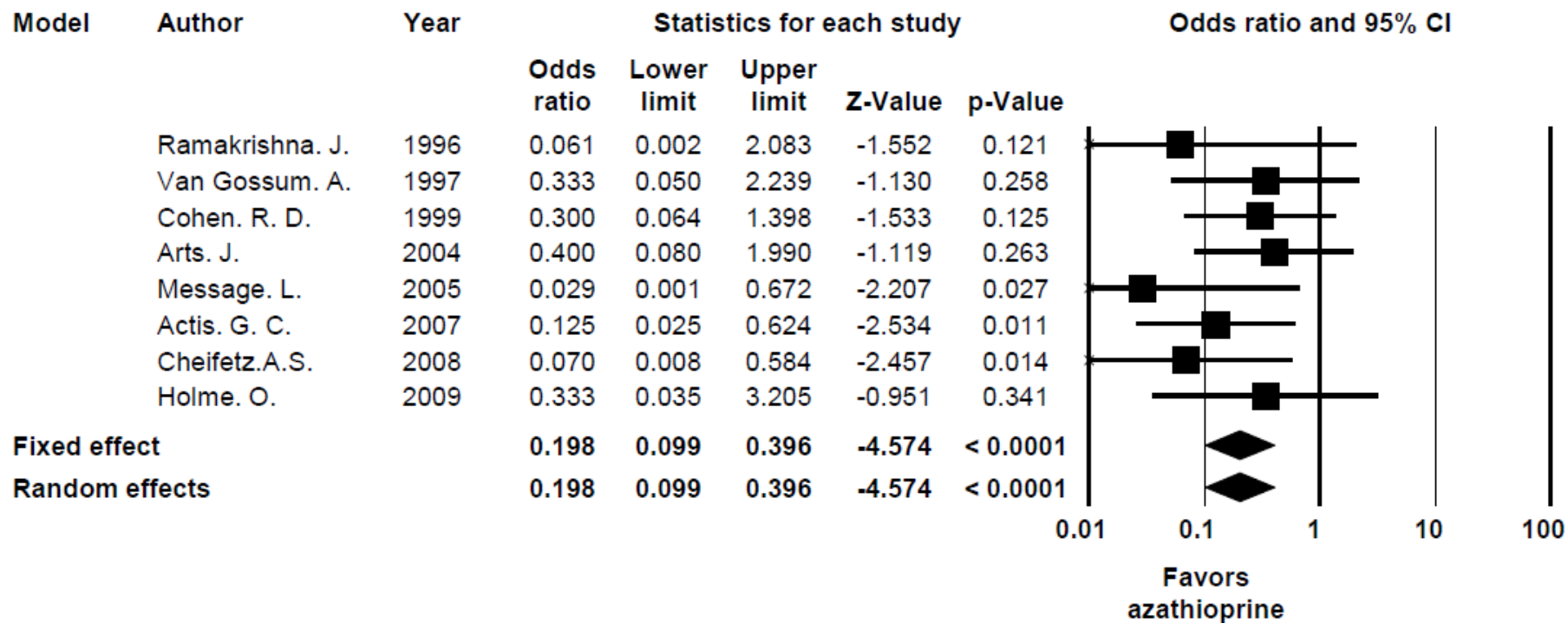
Colectomie à long terme :
33,6% (27,9% à 39,9%)



*Mixed effects analysis

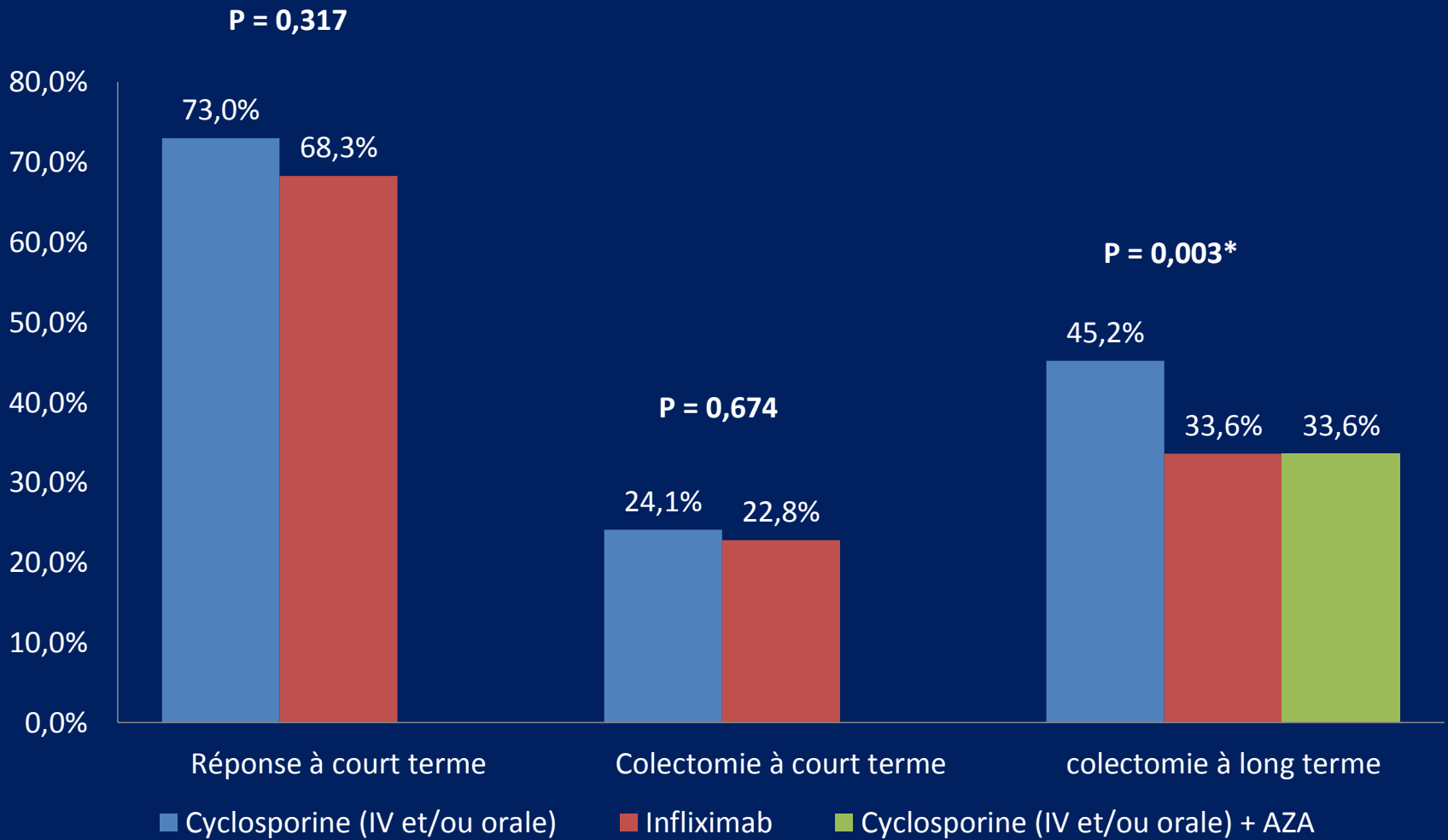
Colectomie à long terme

Bénéfice de l'azathioprine après succès
de la cyclosporine



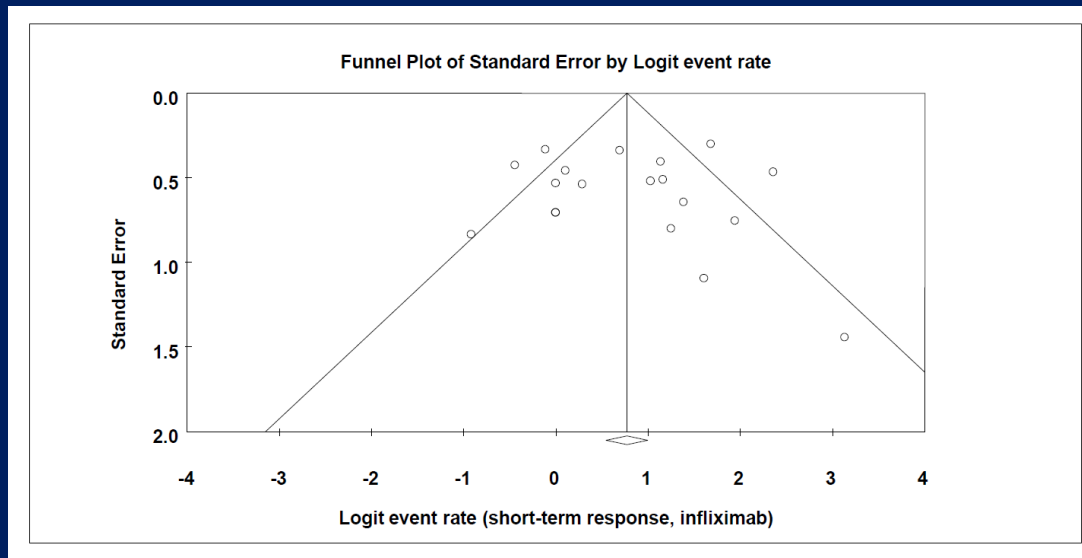
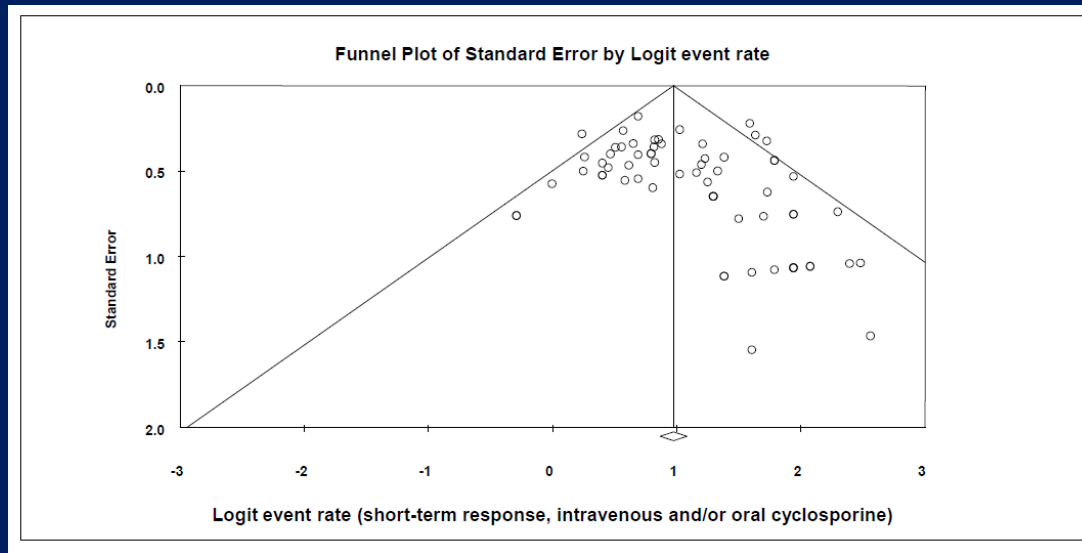
Colectomie à long terme après succès de la cyclosporine
: bénéfique du traitement par azathioprine

OR = 0,198 (95% CI : 0,099 à 0,396)

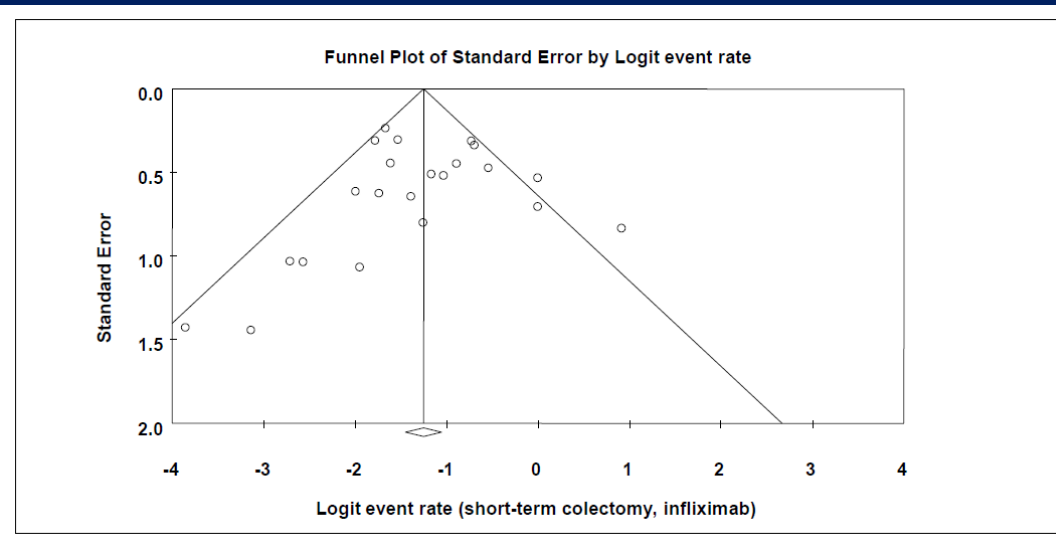
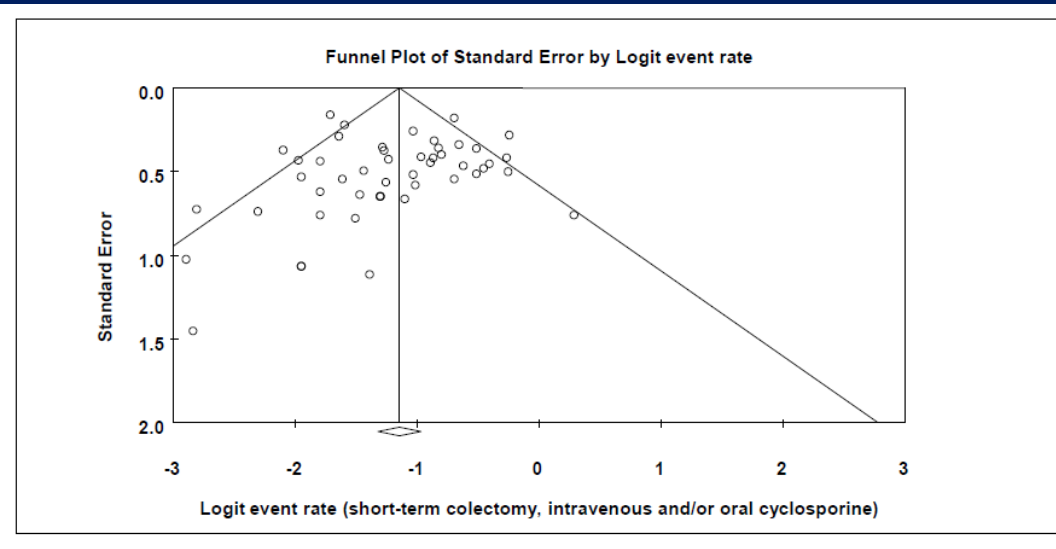


*Mixed effects analysis

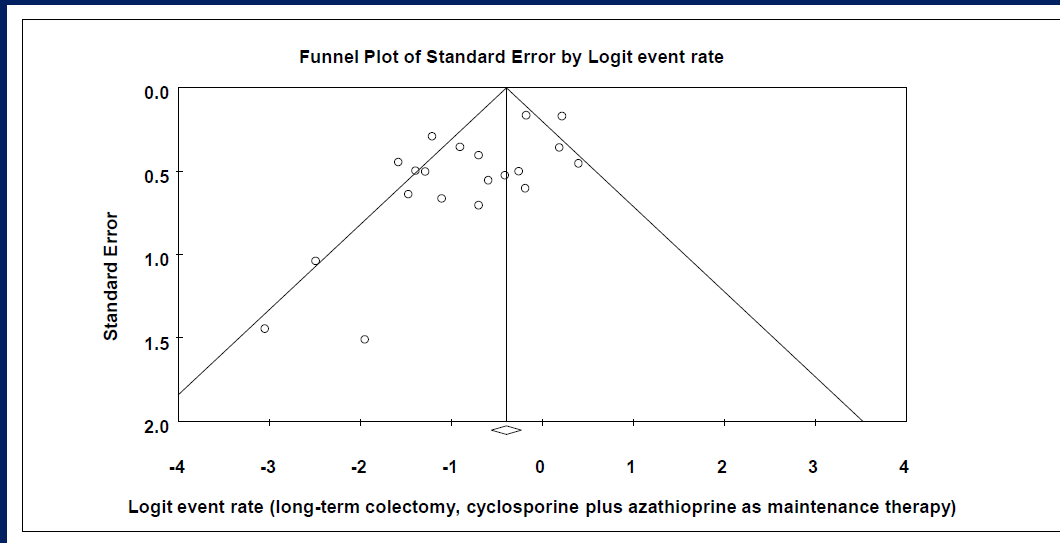
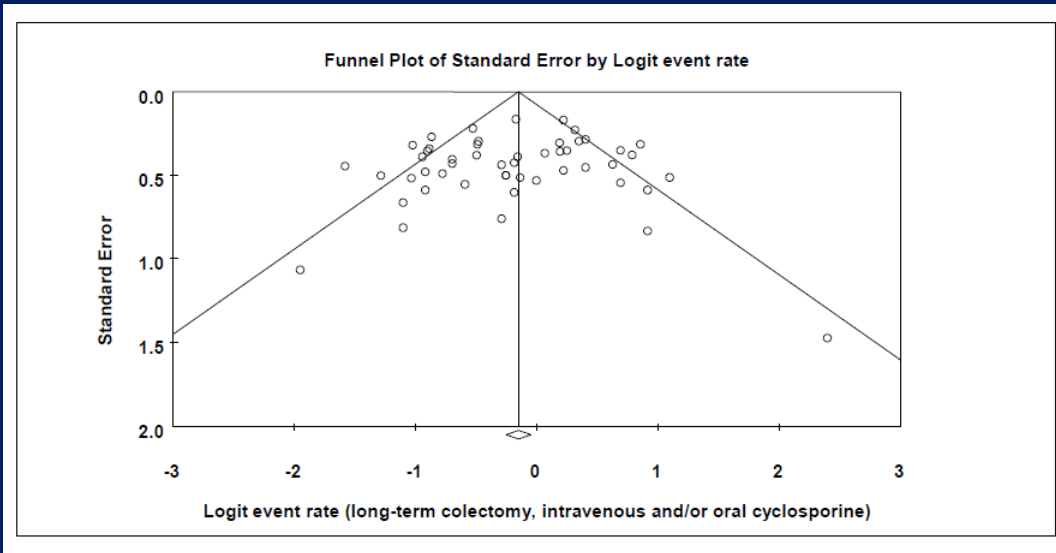
Biais de publication



Réponse à court terme



Colectomie à court terme



Colectomie à long terme

CONCLUSIONS

- Réponse à court terme : IFX = CsA ($\approx 70\%$)
- Colectomie à court terme : IFX = CsA ($\approx 23\%$)
- Absence de relation entre la dose de CsA et les taux de réponse et de colectomie à court terme
- Colectomie à long terme :
 - IFX > CsA (34 % versus 45 %)
 - IFX = CsA + AZA (34 %)

