

Supplementary Appendix

How long does it take to translate research findings into routine healthcare practice? The case of biological drugs for rheumatoid arthritis in Brazil

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Appendix 1 Search strategies - Abatacept for rheumatoid arthritis

Marker event	Data source	Search strategy	Result	Search date
Publication of phase I, II and III clinical trial results	MEDLINE (PubMed)	("Abatacept"[Mesh] OR "Abatacept"[TIAB] OR "LEA29Y"[TIAB] OR " BMS224818"[TIAB] OR " BMS-224818"[TIAB] OR "BMS 224818"[TIAB] OR "Belatacept"[TIAB] OR "Orencia"[TIAB] OR "BMS 188667"[TIAB] OR "BMS-188667"[TIAB] OR "BMS188667"[TIAB] OR "CTLA-4-Ig"[TIAB] OR "CTLA4-Ig"[TIAB] OR "CTLA4-Fc"[TIAB] OR "Nulojix"[TIAB]) AND ("Arthritis, Rheumatoid"[Mesh] OR "Rheumatoid"[TIAB] OR "Arthritis"[TIAB]) AND Therapy/Broad[filter]	969	05/10/2019
Publication of systematic review	MEDLINE (PubMed)	("Abatacept"[Mesh] OR "Abatacept"[TIAB] OR "LEA29Y"[TIAB] OR " BMS224818"[TIAB] OR " BMS-224818"[TIAB] OR "BMS 224818"[TIAB] OR "Belatacept"[TIAB] OR "Orencia"[TIAB] OR "BMS 188667"[TIAB] OR "BMS-188667"[TIAB] OR "BMS188667"[TIAB] OR "CTLA-4-Ig"[TIAB] OR "CTLA4-Ig"[TIAB] OR "CTLA4-Fc"[TIAB] OR "Nulojix"[TIAB]) AND ("Arthritis, Rheumatoid"[Mesh] OR "Rheumatoid"[TIAB] OR "Arthritis"[TIAB]) AND systematic[sb]	83	05/10/2019
Phase I, II and III clinical trial registries	ClinicalTrials.gov	Abatacept OR LEA29Y OR BMS224818 OR BMS-224818 OR BMS 224818 OR Belatacept OR Orcenia OR BMS 188667 OR BMS-188667 OR BMS188667 OR CTLA-4-Ig OR CTLA4-Ig OR CTLA4-Fc OR Nulojix Arthritis	131	05/10/2019

Results – Abatacept for rheumatoid arthritis

Marker event	Date	Reference
Publication of phase I clinical trial results	Not found	Not found
Publication of phase II clinical trial results	06/06/2002	Moreland <i>et al.</i> Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion. <i>Arthritis Rheum</i> 2002;46:1470-1479 DOI: 10.1002/art.10294
Publication of phase III clinical trial results	11/13/2003	Kremer <i>et al.</i> Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. <i>N Engl J Med.</i> 2003 Nov 13;349(20):1907-15. DOI: 10.1056/NEJMoa035075
Publication of systematic review	11/01/2006	Nogid A1, Pham DQ. Role of abatacept in the management of rheumatoid arthritis. <i>Clin Ther.</i> 2006 Nov;28(11):1764-78. DOI: 10.1016/j.clinthera.2006.11.020

Search strategies – Certolizumab for rheumatoid arthritis

Marker event	Data source	Search strategy	Result	Search date
Publication of phase I, II and III clinical trial results	MEDLINE (PubMed)	((("Certolizumab Pegol"[MeSH Terms] OR "Cimzia"[Title/Abstract]) OR "CDP870"[Title/Abstract]) OR "CDP 870"[Title/Abstract]) AND (((("arthritis, rheumatoid"[MeSH Terms] OR "Rheumatoid Arthritis"[Title/Abstract]) OR "Arthritis"[MeSH Terms]) OR "Arthritis"[Title/Abstract])	685	05/14/2020
Publication of systematic review	MEDLINE (PubMed)	(((((certolizumab pegol[MeSH Terms]) OR ("Certolizumab"[Title/Abstract])) OR ("Certolizumab pegol"[Title/Abstract])) OR ("Cimzia"[Title/Abstract]) OR ("CDP870"[Title/Abstract]) OR ("CDP 870"[Title/Abstract])) AND (((("arthritis, rheumatoid"[MeSH Terms] OR "Rheumatoid Arthritis"[Title/Abstract]) OR "Arthritis"[MeSH Terms]) OR "Arthritis"[Title/Abstract])) AND (((("Systematic Review"[Title/Abstract] OR "Review"[Publication Type]) OR "Systematic Reviews as Topic"[MeSH Terms]) OR "Systematic Review"[Publication Type]))	271	05/14/2020
Phase I, II and III clinical trial registries	ClinicalTrials.gov	certolizumab Arthritis, Rheumatoid	85	05/14/2020

Results – Certolizumab for rheumatoid arthritis

Marker event	Date	Reference
Publication of phase I clinical trial results	Not found	Not found
Publication of phase II clinical trial results	10/01/2002	Choy EH, Hazleman B, Smith M, <i>et al.</i> Efficacy of a novel PEGylated humanized anti-TNF fragment (CDP870) in patients with rheumatoid arthritis: a phase II double-blinded, randomized, dose-escalating trial. <i>Rheumatology (Oxford)</i> . 2002;41(10):1133-1137. doi:10.1093/rheumatology/41.10.1133
Publication of phase III clinical trial results	10/30/2008	Keystone E, Heijde Dv, Mason D Jr, <i>et al.</i> 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 [published correction appears in <i>Arthritis Rheum</i> . 2009 May;60(5):1249]. <i>Arthritis Rheum</i> . 2008;58(11):3319-3329. doi:10.1002/art.23964
Publication of systematic review	05/06/2010	Nam JL, Winthrop KL, van Vollenhoven RF, <i>et al.</i> Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA [published correction appears in <i>Ann Rheum Dis</i> . 2011 Aug;70(8):1519]. <i>Ann Rheum Dis</i> . 2010;69(6):976-986. doi:10.1136/ard.2009.126573

Search strategies – Golimumab for rheumatoid arthritis

Marker event	Data source	Search strategy	Result	Search date
Publication of phase I, II and III clinical trial results	MEDLINE (PubMed)	((("golimumab"[Supplementary Concept] OR "golimumab"[Title/Abstract]) OR "Simponi"[Title/Abstract] OR "cnto 148"[Title/Abstract] OR "cnto 148"[Title/Abstract]) AND (((("arthritis, rheumatoid"[MeSH Terms] OR "Rheumatoid Arthritis"[Title/Abstract] OR "Arthritis"[MeSH Terms]) OR "Arthritis"[Title/Abstract]))	779	05/06/2020
Publication of systematic review	MEDLINE (PubMed)	(((((("golimumab"[Supplementary Concept] OR "golimumab"[Title/Abstract]) OR "Simponi"[Title/Abstract] OR "cnto 148"[Title/Abstract] OR "cnto 148"[Title/Abstract])) AND (((("arthritis, rheumatoid"[MeSH Terms] OR "Rheumatoid Arthritis"[Title/Abstract] OR "Arthritis"[MeSH Terms]) OR "Arthritis"[Title/Abstract]))) AND (((("Systematic Review"[Title/Abstract] OR "Review"[Publication Type]) OR "Systematic Reviews as Topic"[MeSH Terms]) OR "Systematic Review"[Publication Type]))	272	05/06/2020
Phase I, II and III clinical trial registries gov	ClinicalTrials.gov	golimumab Arthritis, Rheumatoid	51	05/06/2020

Results – Golimumab for rheumatoid arthritis

Marker event	Date	Reference
Publication of phase I clinical trial results	03/01/2007	Zhou H, Jang H, Fleischmann RM, <i>et al.</i> Pharmacokinetics and safety of golimumab, a fully human anti-TNF-alpha monoclonal antibody, in subjects with rheumatoid arthritis. <i>J Clin Pharmacol.</i> 2007;47(3):383-396. doi:10.1177/0091270006298188
Publication of phase II clinical trial results	03/27/2008	Kay J, Matteson EL, Dasgupta B, <i>et al.</i> Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study [published correction appears in <i>Arthritis Rheum.</i> 2010 Nov;62(11):3518]. <i>Arthritis Rheum.</i> 2008;58(4):964-975. doi:10.1002/art.23383
Publication of phase III clinical trial results	12/09/2008	Keystone EC, Genovese MC, Klareskog L, <i>et al.</i> 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 [published correction appears in <i>Ann Rheum Dis.</i> 2011 Jan;70(1):238]. <i>Ann Rheum Dis.</i> 2009;68(6):789-796. doi:10.1136/ard.2008.099010
Publication of systematic review	01/20/2010	Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis. <i>Cochrane Database Syst Rev.</i> 2010;(1):CD008341. Published 2010 Jan 20. doi:10.1002/14651858.CD008341

Search strategies – Rituximab for rheumatoid arthritis

Marker event	Data source	Search strategy	Result	Search date
Publication of phase I, II and III clinical trial results	MEDLINE (PubMed)	((((((((((("Rituximab"[MeSH Terms] OR "cd20 antibody rituximab"[Title/Abstract])) OR "Mabthera"[Title/Abstract]) OR "idec c2b8 antibody"[Title/Abstract]) OR "idec c2b8"[All Fields]) OR "idec c2b8"[Title/Abstract]) OR "idec c2b8"[Title/Abstract]) OR "GP2013"[Title/Abstract]) OR "Rituxan"[Title/Abstract]) OR "Rituximab"[Title/Abstract]) AND (((("arthritis, rheumatoid"[MeSH Terms] OR "Rheumatoid Arthritis"[Title/Abstract]) OR "Arthritis"[MeSH Terms]) OR "Arthritis"[Title/Abstract]))	2120	05/10/2020
Publication of systematic review	MEDLINE (PubMed)	((((((((((("Rituximab"[MeSH Terms] OR "rituximab"[Title/Abstract] OR "cd20 antibody rituximab"[Title/Abstract])) OR "Mabthera"[Title/Abstract]) OR "idec c2b8 antibody"[Title/Abstract]) OR "idec c2b8 antibody"[Title/Abstract]) OR "idec c2b8"[All Fields]) OR "idec c2b8"[Title/Abstract]) OR "idec c2b8"[Title/Abstract]) OR "GP2013"[Title/Abstract]) OR "Rituxan"[Title/Abstract]) AND (((("arthritis, rheumatoid"[MeSH Terms] OR "Rheumatoid Arthritis"[Title/Abstract]) OR "Arthritis"[MeSH Terms]) OR "Arthritis"[Title/Abstract])) AND (((("Systematic Review"[Title/Abstract] OR "Review"[Publication Type]) OR "Systematic Reviews as Topic"[MeSH Terms]) OR "Systematic Review"[Publication Type]))	738	05/10/2020
Phase I, II and III clinical trial registries	ClinicalTrials.gov	rituximab Arthritis, Rheumatoid	114	05/10/2020

Results – Rituximab for rheumatoid arthritis

Marker event	Date	Reference
Publication of phase I clinical trial results	06/17/2004	Edwards JC, Szczepanski L, Szechinski J, <i>et al.</i> Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. <i>N Engl J Med.</i> 2004;350(25):2572-2581. doi:10.1056/NEJMoa032534
Publication of phase II clinical trial results	04/28/2006	The Efficacy and Safety of Rituximab in Patients With Active Rheumatoid Arthritis Despite Methotrexate Treatment: Results of a Phase IIb Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Trial
Publication of phase III clinical trial results	08/31/2006	Cohen SB, Emery P, Greenwald MW, <i>et al.</i> 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. <i>Arthritis Rheum.</i> 2006;54(9):2793-2806. doi:10.1002/art.22025
Publication of systematic review	10/07/2009	Biologics for rheumatoid arthritis: an overview of Cochrane reviews (Review)

Search strategies – Tocilizumab for rheumatoid arthritis

Marker event	Data source	Search strategy	Result	Search date
Publication of phase I, II and III clinical trial results	MEDLINE (PubMed)	((((((((((((tocilizumab[Supplementary Concept]) OR ("tocilizumab"[Title/Abstract])) OR ("RHPM-1"[Title/Abstract])) OR ("RG-1569"[Title/Abstract])) OR ("R-1569"[Title/Abstract])) OR ("MSB11456"[Title/Abstract])) OR ("MSB-11456"[Title/Abstract])) OR ("atlizumab"[Title/Abstract])) OR ("MRA"[Title/Abstract])) OR ("RO-4877533"[Title/Abstract])) OR ("Actemra"[Title/Abstract])) OR ("roactemra"[Title/Abstract])) OR ("roactemra"[Title/Abstract])) AND (((("arthritis, rheumatoid"[MeSH Terms] OR "Rheumatoid Arthritis"[Title/Abstract] OR "Arthritis"[MeSH Terms] OR "Arthritis"[Title/Abstract]))	1921	05/09/2020
Publication of systematic review(PubMed)	MEDLINE (PubMed)	((((((((((((((((tocilizumab[Supplementary Concept]) OR ("tocilizumab"[Title/Abstract])) OR ("RHPM-1"[Title/Abstract])) OR ("RG-1569"[Title/Abstract])) OR ("R-1569"[Title/Abstract])) OR ("MSB11456"[Title/Abstract])) OR ("MSB-11456"[Title/Abstract])) OR ("atlizumab"[Title/Abstract])) OR ("MRA"[Title/Abstract])) OR ("RO-4877533"[Title/Abstract])) OR ("Actemra"[Title/Abstract])) OR ("roactemra"[Title/Abstract])) OR ("roactemra"[Title/Abstract])) AND (((("arthritis, rheumatoid"[MeSH Terms] OR "Rheumatoid Arthritis"[Title/Abstract] OR "Arthritis"[MeSH Terms] OR "Arthritis"[Title/Abstract])) AND (((("Systematic Review"[Title/Abstract] OR "Review"[Publication Type] OR "Systematic Reviews as Topic"[MeSH Terms] OR "Systematic Review"[Publication Type]))	526	05/09/2020
Phase I, II and III clinical trial registries	ClinicalTrials.gov	"Arthritis, Rheumatoid" "tocilizumab" OR "roactemra"	218	05/09/2020

Results – Tocilizumab for rheumatoid arthritis

Marker event	Date	Reference
Publication of phase I clinical trial results	12/12/2002	Choy EH, Isenberg DA, Garrood T, <i>et al.</i> Therapeutic benefit of blocking interleukin-6 activity with an anti-interleukin-6 receptor monoclonal antibody in rheumatoid arthritis: a randomized, double-blind, placebo-controlled, dose-escalation trial. <i>Arthritis Rheum.</i> 2002;46(12):3143-3150. doi:10.1002/art.10623
Publication of phase II clinical trial results	12/12/2002	Choy EH, Isenberg DA, Garrood T, <i>et al.</i> Therapeutic benefit of blocking interleukin-6 activity with an anti-interleukin-6 receptor monoclonal antibody in rheumatoid arthritis: a randomized, double-blind, placebo-controlled, dose-escalation trial. <i>Arthritis Rheum.</i> 2002;46(12):3143-3150. doi:10.1002/art.10623
Publication of phase III clinical trial results	05/03/2007	Nishimoto N, Hashimoto J, Miyasaka N, <i>et al.</i> 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. <i>Ann Rheum Dis.</i> 2007;66(9):1162-1167. doi:10.1136/ard.2006.068064
Publication of systematic review	10/28/2008	Plushner SL. Tocilizumab: an interleukin-6 receptor inhibitor for the treatment of rheumatoid arthritis. <i>Ann Pharmacother.</i> 2008;42(11):1660-1668. doi:10.1345/aph.1L268

Appendix 2 Marker event dates of the five biological DMARDs

Step	Marker	Drugs				
		abatacept	certolizumab	golimumab	rituximab	tocilizumab
T1	Publication of the results of the first phase I clinical trial	N/F	N/F	3/1/2007	6/17/2004	12/12/2002
	Publication of the results of the first phase II clinical trial	6/6/2002	10/1/2002	3/27/2008	4/28/2006	12/12/2002
	Publication of the results of the first phase III clinical trial	11/13/2003	10/30/2008	12/9/2008	8/31/2006	5/3/2007
	Approval of the first health registration by Anvisa	6/25/2007	5/23/2011	4/11/2011	7/3/2006	1/19/2009
	Approval of the first health registration by FDA	12/23/2005	5/13/2009	4/24/2009	2/28/2006	1/8/2010
	Approval of the first health registration by EMA	5/21/2007	10/1/2009	10/1/2009	9/29/2006	1/15/2009
T2	Publication of the first review with systematic search	11/1/2006	5/6/2010	1/20/2010	10/7/2009	10/28/2008
	Assessment request from Conitec	3/14/2012	1/26/2012	6/21/2012	5/16/2012	5/16/2012
	Conitec initial recommendation	6/1/2012	6/1/2012	6/1/2012	6/1/2012	6/1/2012
	Conitec final decision	7/5/2012	7/5/2012	7/5/2012	7/5/2012	7/5/2012
	Ministry of Health decision	9/11/2012	9/11/2012	9/11/2012	9/11/2012	9/11/2012
	Guideline, manual, guide, or protocol publication	6/28/2013	6/28/2013	6/28/2013	6/28/2013	6/28/2013
T3	Registration of the first purchase after incorporation	1/30/2013	1/29/2013	4/24/2013	3/7/2013	5/17/2013
	First dispensing record	4/15/2013	8/15/2013	7/15/2013	4/15/2013	6/15/2013

N/F: not found.