Daclizumab in multiple sclerosis

Francisco C. Pérez-Miralles

Introduction. Daclizumab is a monoclonal antibody directed against the CD25 subunit of the interleukin-2 receptor, investigated as a disease-modifying therapy in relapsing-remitting multiple sclerosis. The present review addresses how the drug was developed, the known mechanism of action of the drug and the up-to-date data of efficacy and safety.

Development. Daclizumab has shown superiority in prevention of relapses against placebo and low-dose interferon beta-1a at a level that puts it on par with the rest of current first-line drugs. The effect on the progression of the disease and on neurodegeneration parameters, however, is not clear. On the other hand, it presents safety problems (mainly risk of autoimmunity phenomena including fulminant hepatopathy and encephalitis) that have supposed eventually its withdrawn from marketing. Daclizumab introduces a new mechanism of action through the blocking of a key interleukin in immune regulation and its effect on a population of cells with regulatory ability, such as the NK CD56(bright) cells.

Conclusions. Daclizumab has shown efficacy in slowing the inflammatory process of multiple sclerosis, although the appearance of potentially serious side effects has not allowed its use to significantly impact current clinical practice. The development of new drugs in multiple sclerosis must be contingent on maintaining or improving the risk-benefit profile with respect to those already in use.

Key words. Daclizumab. Interleukine 2. Monoclonal antibody. Multiple sclerosis. NK cell. Safety.

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). Its cause at present is unknown and environmental and genetic factors are probably involved. Due to the natural evolution of the disease, a high percentage of patients will develop a neurological disability in the following years of diagnosis [1].

Fortunately, over time, drugs have been developed that can modify the natural history of the disease (disease-modifying therapies, DMT), thus progressively abandoning an era of therapeutic nihilism [2]. Currently, we have several DMT options, with different degrees of efficacy and adverse reaction profile, usually in direct relation [3], with specific recommendations for use for each of them, based on scientific consensus [4].

The reason for using daclizumab in MS is derived from the concept of this disease as an autoimmune disease mediated by CD4+ T cells. Daclizumab is a humanized monoclonal antibody directed against the so-called Tac epitope of CD25 of the interleukin 2 receptor (IL-2R), in such a way that it blocks high affinity IL-2R, thus preventing the maturation of autoreactive activated CD25+ T cells.

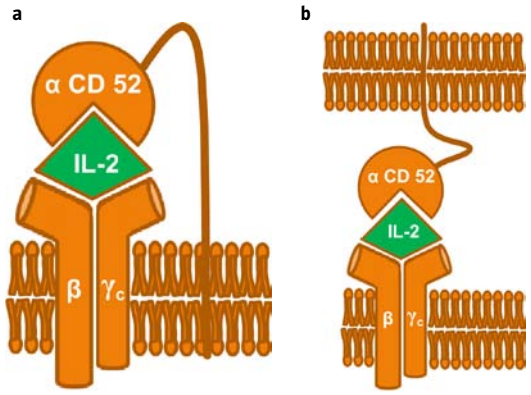
Proposed mechanisms of action for daclizumab

It was initially thought that the main mechanism of action was based on the blockade of IL-2 through CD25, preventing the maturation of autoreactive T lymphocytes. However, it has been found that the effects of inhibiting IL-2 in vivo are much more complex.

IL-2 is produced mainly by activated CD4+ lymphocytes and, to a lesser extent, by activated CD8+ lymphocytes. However, other populations such as dendritic cells and NK lymphocytes also secrete IL-2 [5,6].

IL-2R is a receptor formed by several subunits (α, β, γ_c), whose interactions with each other form different receptor subtypes: high, intermediate and low affinity (Fig. 1) [7]. Intermediate affinity IL-2R is formed by the β and γ_c chains. The α subunit (CD25) is the low affinity receptor and does not induce any cellular response by itself, but it helps to capture IL-2 on the cell surface when it binds to the rest of subunits. The binding of CD25 to the rest of subunits to form the high affinity IL-2R can be done through the membrane of the same cell ('cis' binding), or from the membrane of

Figure 1. Schematic representation of the interleukin 2 receptor. The cis presentation (a) is typical in regulatory T lymphocytes (CD4+CD25+ Foxp3+), and the trans presentation (b) in CD4+ or CD8+ T lymphocytes during antigenic presentation with a dendritic cell, in which the latter provides the α subunit (CD25).



a dendritic cell during the presentation of antigen ('trans' binding) [8].

Daclizumab acts on effector T cells by inhibiting their proliferation by blocking the binding with high affinity IL-2R. However, this effect hardly produces a perceptible decrease in peripheral CD4+ and CD8+ T cell counts [9], so its in vivo effects should be sought in other mechanisms (Fig. 2).

It has been observed that daclizumab therapy produces an increase of up to 7-8 times the number of $CD56^{bright}$ NK cells circulating in peripheral blood and cerebrospinal fluid; these cells lack CD25, but they do have the conformation of intermediate affinity IL-2R. Interestingly, this type of NK cell seems to possess immune regulatory properties and has the ability to mediate cytotoxicity and eliminate autologous activated T lymphocytes [10] by releasing granzyme K, which induces apoptosis of these cells [11], and it is suspected that could also act on resting microglia [12]. It has been described that its population also expands during the first trimester of pregnancy, so it may be involved in the mechanisms of materno-fetal immunological tolerance [13].

In addition, the increase in $CD56^{bright}$ NK cell population correlates with a decrease in lymphoid tissue-inducing cells, another lymphoid population of innate lymphoid cells of special interest in MS for their ability to form meningeal ectopic lymphoid follicles [14-16].

Notwithstanding, a reduction of up to 40% in the levels of regulatory T lymphocytes (CD4+ CD25+ Foxp3+) has also been observed. Although on one hand this reduction do not seem to intervene with the clinical results or with the appearance of complications [17], on the other it is known that the deletion of the gene coding for CD25 in humans has been related to the appearance of autoimmunity and lymphoproliferation phenomena [18,19], and it is possible that daclizumab enhances autoimmunity phenomena by an undesirable effect on this lymphocyte subpopulation that regulates immune tolerance [20].

Development of daclizumab as therapy for multiple sclerosis and efficacy data in the main studies

Daclizumab is derived from the development of a murine monoclonal antibody investigated by the National Institute of Health / National Cancer Institute of the United States [21]. It was the first commercialized humanized monoclonal antibody [22-25], produced by PDL BioPharma and marketed by Roche Pharma (Zenapax®).

Initially, it was studied as a therapy against leukaemia caused by the human T-cell lymphotropic virus type I (HTLV-I) [24], but was finally approved with the indication to prevent rejection after allogeneic kidney transplantation [26] by the United States Food and Drug Administration (FDA) in 1997 and for allogeneic solid organ transplantation in Europe in 1999, as a combination therapy with steroids and ciclosporin [27,28]. It has also been tested in tropical spastic paraparesis by HTLV-I, where it showed reduced viral load [29], and in uveitis of non-infectious origin [30].

The first phase I-II trials in MS were open-label, non-blinded, as add-on therapy to interferon β (IFNβ), in patients who presented an inadequate response to any formulation of IFNβ for use in MS [31,32]. Although with the limitations of uncontrolled studies to extract efficacy data, a reduction in magnetic resonance (MR) greater than 70% in the appearance of new lesions with enhancement after gadolinium in T_1-weighted sequences was observed in these studies (NGdL) during the period of combination therapy at a dose of 1 mg/kg monthly iv daclizumab for 6 months. In the follow-up studies, a large part of the patients remained on monotherapy with daclizumab, although a third required either continuing therapy with IFNβ or using a higher dose of daclizumab [32,33]. Another open-label, unblinded phase II trial in patients who had not received previous therapies, showed similar results [34].

However, the production of daclizumab was interrupted in 2009 , according to the pharmaceutical company, in view of the availability of alternative therapies and the waning demand for the drug in the market, but not due to safety problems [35]. Indeed, although in the field of solid organ transplantation the strategy of blocking IL-2R through the anti-CD25 mechanism (since the withdrawn of daclizumab, with the chimeric monoclonal antibody basiliximab) remains currently a valid option [36], increasingly, classical immunosuppression strategies that induce lymphocyte depletion such as antitimocitic globulin are preferred, especially in patients considered to be at high risk [37]. Although the development of daclizumab was interrupted both in the field of transplantation and in other diseases, such as bronchial asthma, the results in MS allowed to continue its development by Facet Biotech (company to which PDL BioPharma transferred its projects) together with Biogen Idec [38,39].

A randomized, double-blind, placebo-controlled, 6-month phase II study with 2 arms of active treatment of subcutaneous daclizumab at 2 mg/kg every 2 weeks and 1 mg/kg every 4 weeks in combination with the formulation of IFNβ in which participants were being previously treated was designed (CHOICE study). This study showed that, compared to being treated only with IFNβ, the high and low dose arms reduced the number of NGdL by 72% and 25%, respectively. The low dose arm, however, did not reach a statistically significant result (p = 0.051). As secondary objectives, this study measured the annualized rate of relapses, observing a reduction of 43% and 32% in the high and low dose groups, respectively, although without reaching statistical significance. Initially, it was thought that the dose of 1 mg/kg would be sufficient to block all of the CD25 in peripheral blood [40]. The increased efficacy of the high-dose arm led to the conclusion that saturation of CD25 occurred not only in peripheral blood, but also in those places where specific activation of the T lymphocyte occurs, such as the lymphoid organs and in those tissues with inflammation, even in the same parenchyma of the central nervous system [41].

Pivotal studies in daclizumab

After the CHOICE study, a modification of the chemical structure of daclizumab was developed by a 'high-yield procedure' (daclizumab-HYP) in which the glycosylation pattern of the antibody was changed, conserving the original amino acid sequence. This modification affects how the antibody binds to Fc receptors, thus improving tolerance by reducing antibody-dependent cellular cytotoxicity and complement fixation, but without modifying the direct interaction with the CD25 receptor with respect to the original daclizumab [42]. It was this last formulation, which allows the subcutaneous use of daclizumab once every 4 weeks, the one in which the rest of the studies continued. Subsequently, this new formulation has been called 'daclizumab beta'. For simplicity, we will keep the term daclizumab, as it is the one that has transcended to the final summary of the product characteristic report of the drug.

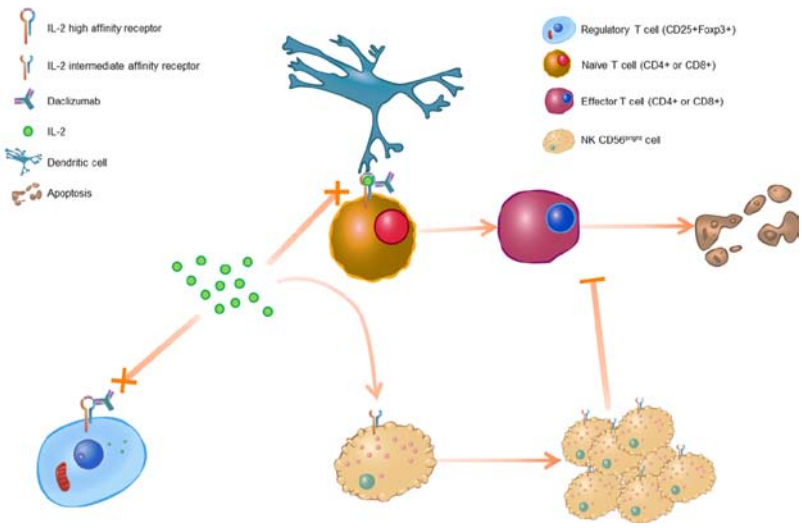


Figure 2. Schematic of the main mechanisms of action of daclizumab. Daclizumab inhibits the binding of interleukin-2 (IL-2) to the high affinity receptor of IL-2, thus preventing the maturation of T lymphocytes in mature effector T lymphocytes. This produces a relative availability of IL-2 over the intermediate affinity receptor, present in NK CD56^{bright} cells, whose population is expanded. The regulatory effect of this population can thus compensate for the potential effect of daclizumab on the inhibition of regulatory T lymphocytes.

SELECT study (daclizumab versus placebo)

The following study explored the efficacy of daclizumab monotherapy in a population of patients with MS who did not receive previous DMT for the most part.

The active treatment arms of this study, called SELECT, were 150 mg and 300 mg subcutaneously every 4 weeks for 1 year. On this occasion, the dose of 150 mg showed a similar efficacy, if not better, than the highest dose; both arms of active treatment reduced the annualized rate of relapses, the proportion of patients who had a relapse during

Table I. Summary of the clinical and radiological efficacy data from the pivotal studies of daclizumab.

	SELECT [a] [27]			DECIDE [b] [28]		
	Placebo (n = 196)	DCL 150 mg (n = 201)	p	Interferón-β 1a [c]	DCL 150 mg	p
Annualized relapse rate (95% CI)	0.46 (0.37-0.57)	0.21 (0.16-0.29)	< 0.0001	0.39 (0.35-0.44)	0.22 (0.19-0.24)	< 0.001
	Relative risk reduction: 46%			Relative risk reduction: 45%		
Relapse free	65%	81%	< 0.0001	51%	67%	ns [d]
	HR: 0.45 (0.30-0.67)	NNT: 6 (4-13)		HR: 0.59 (0.50-0.69)	NNT: ns [d] 6 (5-8)	
12-weeks CDW	13%	6%	0.021	20%	16%	ns
	HR: 0.45 (0.30-0.67)	NNT: 14 (8-71)		HR: 0.84 (0.66-1.07)	NNT: ns 34 (16-81)	
New active lesions (95% CI)	8.1 (6.7-9.9)	2.4 (2.0-3.0)	< 0.0001	9.4 (8.5-10.5)	4.3 (3.9-4.8)	< 0.001
	Relative risk reduction: 70%			Relative risk reduction: 54%		
NGdL (95% CI)	1.4 (1.1-1.8) [e]	0.3 (0.2-0.4) [e]	< 0.0001	1.0 (0.8-1.2)	0.4 (0.3-0.5)	< 0.001
	Relative risk reduction: 79%			Relative risk reduction: 60%		
PBVC (95% CI)	–0.74 (–0.87 to –0.61) [e]	–0.79 (–0.91 to –0.67) [e]	ns	–0.59 [f]	–0.56 [f]	< 0.001
	Relative risk reduction: –6,8%			Relative risk reduction: 4,4%		

95% CI: 95% confidence interval; CDW: percentage of patients with confirmed disability worsening; DCL: daclizumab; HR: hazard ratio; NGdL: new gadolinium-enhancing lesions; ns: statistically not significant; NNT: number needed to treat in order to prevent an event; PBVC: percentage of brain volume change. [a] Only results of the daclizumab 150 mg arm at week 52 are shown; [b] Results at week 144; [c] Interferon-β1a 30 μg intramuscular weekly; [d] Results considered as statistically not significant in the hierarchical analyses, as the secondary endpoint in 12-week confirmed disability worsening was not reached; [e] 95% confidence interval was inferred through the standard deviation showed in the original report; [f] 95% confidence interval not showed in the original report and cannot be inferred through the published data.

treatment, the proportion of patients who experienced an increase in the expanded disability status scale (EDSS) and in the number of active lesions in T_2-weighted sequences (new or enlarging-NAcL) in MRI [43] (Table 1; Fig. 3).

DECIDE study (daclizumab 150 mg versus interferon-β1a 30 μg intramuscular)

Finally, a randomized, multicenter, double-blind, double-dummy active control (IFNβ1a 30 μg intramuscular weekly), parallel groups (daclizumab sc / placebo im or placebo sc / IFNβ1a im) study, the DECIDE study, was performed [44]. Daclizumab 150 mg sc every 4 weeks showed a reduction in the annualized relapse rate of 45% with respect to low dose IFNβ1a (Table I; Fig. 3). There was also a 54% reduction in the number of NAcL in the MRI scan of week 96 ($p < 0.001$), but no statistically significant differences were found in the proportion of patients who had a 12-week confirmed worsening of their disability (16% in the daclizumab group and 20% in the IFNβ1a group).

As exploratory objectives, it should be noted that the reduction in the annualized relapse rate was consistent throughout the study (from baseline to weeks 48 and 96), that the effect on the worsening of the 24-week confirmed worsening of disability in the last visit week 144 did show significant differences (18% in the placebo group and 13% in the daclizumab group; $p = 0.03$) and that differences were detected in the changes of the multiple sclerosis functional composite scale (MSFC) and its components (25-step walk test, nine hole-peg test, PASAT-3), as well as in the symbol-digit modalities test (SDMT) in week 96 and not in week 48; The clinical value of this last result, although statistically significant, is uncertain given the size of the effect (change of 0.055 in the MSFC score in the placebo group and 0.071 in the daclizumab group). No differences were found in the evolution of the EDSS

in weeks 48 or 96, or differences in the percentage of patients who had a sustained improvement in disability.

In terms of exploratory results of MR parameters, daclizumab showed radiological efficacy data from the first MRI scan of week 24, with reduction in the number and volume of NAcL at week 24 and in the number of NGdL in MRI scans in weeks 48 and 96. Regarding markers of degeneration, daclizumab has been shown to reduce both the week 48 and 96 the appearance of new hypointense lesions in T_1-weighted sequences (the so-called 'black holes'), with a reduction of 52% in their number in week 96.

The behaviour of the changes in brain volume is worth mentioning separately. After the introduction of daclizumab and IFNβ1a im, an accelerated volume reduction was observed in the first 6 months with respect to the baseline situation, which reached –0.668% in the daclizumab group and –0.739% in the IFNβ1a group (p = 0.03). The percentages of brain volume change (PBVC) from baseline to week 96 and from week 24 to week 96 were very similar. Returning to the results of the SELECT study, in this study a tendency for a greater decrease in the brain volume vs. placebo was detected in the first 6 months of treatment with daclizumab, decrease that was maintained during the 52 weeks that the study lasted. This seems to indicate that the phenomenon of pseudoatrophy, present in many other drugs in MS, acts during the first months of treatment and stabilizes later [45-50]. All the same, it is unknown whether the meaning of a relative reduction of 4.4% of loss of PBVC compared to IFNβ1a im, although statistically significant, is clinically relevant.

Results of extension studies and post-hoc analysis

Both the SELECT and the DECIDE studies have been followed by extension studies, but not in the CHOICE study. The SELECTION study (n = 517), one year long, collected those patients who completed the SELECT study (n = 621). In this study, the patients were re-randomized: those from the placebo arm were re-randomized to take daclizumab 150 mg or 300 mg sc monthly, and those who took daclizumab (either at a dose of 150 mg or 300 mg) were re-randomized to keep the same dose or temporarily stop treatment for 6 months and continue at the same dose [51]. Those patients who completed the follow-up period of SELECTION were offered to continue with daclizumab 150 mg sc monthly under the SELECTED study (n = 410).

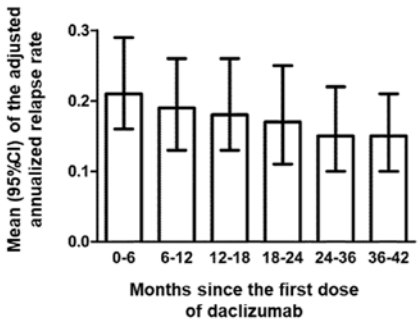
Figure 3. Schematic of the design of the pivotal studies of daclizumab (a) and their extension studies (b). DCL: daclizumab; PCB: placebo run-in phase before daclizumab.

Finally, those patients who completed the DECIDE study were offered to participate in the extension phase called EXTEND, for which there are no published results yet.

The results at 3 years of the SELECTED study showed that daclizumab maintained the annualized relapse rate of around 0.2 over 3 years (Fig. 4) [52]. Recently, the up to 6 years results of the SELECTED study were announced in the 7th Joint Meeting of the ECTRIMS-ACTRIMS of 2017, held in Paris, noting that annualized relapse rates may decrease to 0.10 in patients who exceed 336 weeks of follow-up [53]. However, these data should be interpreted with caution, since open extension studies are exposed to an important selection bias (only 95 patients exceeded 336 weeks of follow-up) and it is not possible to discern the actual efficacy of the drug from the natural MS history. However, the experience of the SELECTED study does not seem to indicate that the drug loses its effect in the short to medium term.

A post hoc study based on the SELECT trial showed that daclizumab is also effective in a subgroup of patients defined as having 'high activity'

Figure 4. Annualized relapse rate evolution during the SELECTED study [36]. 95% CI: 95% confidence interval.



(at least 2 relapses in the year prior to randomization and presence of NGdL on baseline MRI scan), reducing the relapse rate by 50% compared with placebo, similar to the 'lower activity' group (51% reduction) [54].

A recent post hoc work of subgroups of the DECIDE study showed that those patients aged ≤ 35 years and with a volume of hyperintense T_2 lesions greater than or equal to the median in baseline MRI were more likely to respond better for three exploratory measurements (24-week confirmed disease progression, 24-week sustained MSFC progression, clinically meaningful worsening in MSIS-29 PHYS score) with daclizumab than with IFNβ1a im [55]. An improvement over IFNβ1a in the SDMT values and a lower proportion of patients who worsened ≥ 3 points in the SDMT at week 96 was also observed [56].

A study is under way to evaluate the efficacy of daclizumab to prevent the reactivation of the disease after the withdrawal of natalizumab (SUSTAIN study, ClinicalTrials.gov, identification code NCT-02881567), although there is already a sole report of a case of failure of this therapy to prevent rebound phenomena, that required therapeutic rescue with alemtuzumab [57].

Security data

The rate of occurrence of adverse events (AE) has been similar both to placebo and to low-dose IFNβ1a and, for the most part, these were mild or moderate. However, there has been a higher incidence of serious adverse reactions (infections, skin reactions and liver disorders). Safety data is also available for up to 6 years of follow-up from the first dose of daclizumab from the SELECTED and EXTEND extension studies [53,58]. Table II summarizes the AE incidences found in the main studies and their respective extension phases.

Infections

The infections that occurred most frequently in patients treated with daclizumab vs. placebo or IFNβ1a were those of the upper (nasopharyngitis, influenza) and lower (bronchopneumonia) respiratory tract. Serious infections occurred in 3-4% of patients treated with daclizumab, compared to none in the SELECT study control group and 2% of patients treated with IFNβ1a. In general, the infections were managed in a conventional manner and for the most part did not require the suspension of the drug.

There have been no reports of progressive multifocal leukoencephalopathy or a clear increase in opportunistic infections in patients with MS with daclizumab. The appearance of herpes group viral infections was similar in patients with daclizumab and in the control groups with placebo or IFNβ1a. No data are available on the possibility of reactivation of infectious hepatitis B or C virus, since the participation of patients with chronic or active infections was specifically excluded. On the other hand, cases of tuberculosis have been described in extension studies, at least one case in the SELECTED study [52], and 3 in EXTEND [58].

Liver disease

Although the rate of elevation of liver enzymes has been similar in patients treated with daclizumab as with placebo or IFNβ1a, the occurrence of enzymatic elevations above 5 times the normal values was higher in the daclizumab group in both pivotal studies.

The European Medicines Agency (EMA) has reviewed the incidence of severe hepatic impairment –alanine aminotransferase or aspartate aminotransferase (ALT/AST) levels greater than or equal to 5 times the upper limit of normal values– in all daclizumab studies (not only the pivotal studies and their extensions) and has observed that it is superior to the one initially described, and that it reaches 1.7%. At the date of this review, two deaths due to fulminant autoimmune hepatitis have been described, one case of non-fatal acute liver failure taking concomitantly valproic acid, carbamazepine and herbal products and one case of AST/ALT ele-

Table II. Incidence of the most relevant adverse events in the pivotal studies of daclizumab and in their extension studies.

		SELECT [27]			SELECTION [35]		SELECTED [37] [a]	DECIDE [28] [b]		EXTEND [58]
		PCB (*n* = 204)	DCL 150 mg (*n* = 208)	DCL 300 mg (*n* = 209)	DCL 150 mg [g] (*n* = 258)	DCL 300 mg [h] (*n* = 259)	DCL 150 mg (*n* = 410) [a]	IFN-β1a (*n* = 922)	DCL 150 mg (*n* = 919)	DCL 150 mg (*n* = 1516) [c]
All AE		161 (79%)	151 (73%)	159 (76%)	188 (73%)	180 (69%)	358 (87%)	842 (91%)	838 (91%)	1393 (92%)
Severe AE		53 (26%)	32 (15%)	36 (17%)	48 (19%)	37 (14%)	148 (36%)	194 (21%)	221 (24%)	ND
Severe AE excluding relapses		12 (6%)	15 (7%)	19 (9%)	19 (7%)	15 (6%)	105 (26%)	88 (10%)	142 (15%)	308 (20%)
DCL withdrawns due to AE		ND	ND	ND	12 (5%)	12 (5%)	91 (22%)	112 (12%)	142 (15%)	327 (22%)
Neoplasms		1 (< 1%) [j]	1 (< 1%) [k]	2 (< 1%) [l]	0	1 (< 1%) [m]	10 (2%) [n]	8 (1%) [ñ]	7 (1%) [o]	12 (< 1%) [p]
Demises		0	1 (< 1%) [q]	0	0	1 (< 1%) [r]	0	4 (< 1%) [s]	1 (< 1%) [t]	2 (< 1%) [u]
AE of special interest	Infections	89 (44%)	104 (50%)	112 (54%)	104 (40%)	105 (40%)	252 (61%)	523 (57%)	595 (65%)	1017 (67%)
	Severe AE	0	6 (3%)	3 (1%)	8 (3%)	5 (2%)	23 (6%)	15 (2%)	40 (4%)	77 (5%)
	URTI	54 (26%)	61 (29%)	65 (31%)	55 (21%)	50 (19%)	139 (34%) [d]	321 (35%)	375 (40%)	813 (54%)
	Oral herpes	10 (5%)	10 (5%)	13 (6%)	ND	ND	19 (5%) [d]	ND	ND	ND
	UTI	ND	ND	ND	ND	ND	31 (8%) [d]	98 (11%)	96 (10%)	177 (12%)
	Skin	27 (13%)	38 (18%)	45 (22%)	51 (20%)	48 (19%)	157 (38%)	176 (19%)	344 (37%)	637 (42%)
	Severe AE	0	2 (< 1%)	3 (1%)	3 (1%)	3 (1%)	18 (4%)	1 (< 1%)	14 (2%)	39 (3%)
	Liver	71 (35%) [e]	70 (34%) [e]	76 (36%) [e]	80 (31%) [e]	93 (36%) [e]	104 (25%)	130 (14%)	144 (16%)	282 (19%)
	AST/ALT ≥ 3 ULN	ND	ND	ND	ND	ND	60 (15%)	80 (9%)	96 (10%)	183 (13%)
	AST/ALT 3-5 ULN	6 (3%)	7 (3%)	6 (3%)	3 (1%)	7 (3%)	ND	ND	ND	ND
	AST/ALT ≥ 5 ULN	1 (< 1%)	9 (4%)	8 (4%)	3 (1%)	8 (3%)	37 (9%)	31 (3%)	59 (6%)	121 (8%)
	AST/ALT ≥ 3 ULN and BLB ≥ 2 ULN	ND	ND	ND	ND	ND	2 (< 1%)	1 (< 1%)	7 (1%)	ND
	Skin reaction in injection site	3 (1%)	4 (2%)	4 (2%)	5 (2%)	9 (3%)	ND	102 (11%) [f]	96 (10%) [f]	ND
	Autoimmunity [i]	0	0	2 (< 1%) [v]	0	4(2%) [w]	ND	ND	ND	3 (< 1%) [x]
	Linfadenopathy	0	0	1 (< 1%)	ND	ND	28 (7%)	ND	ND	143 (9%)

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate transaminase; BLB: bilirubine; DCL: daclizumab; IFNβ1a: interferon-β1a 30 µg intramuscular weekly; URTI: upper respiratory tract infection; UTI: urinary tract infection; ND: not reported in the original publication; PCB: placebo; ULN: upper level of normal. [a] Data from all patients included during the 6-years follow-up; [b] Data from all patients included during the 3-years follow-up; [c] Data from all patients that received at least one dose of daclizumab during the 6-years follow-up period, including those who participated in the DECIDE study and did not participate in the EXTEND study; [d] Data obtained from a previous publication up to 3-years of follow-up [36], since there is no data of 6 years of follow-up; [e] Data showed in the original publication as elevation of liver enzymes and not specifically as liver adverse events; [f] Data showed in the original publication as 'injection-site pain'; [g] Grouped data including all patients that were randomized to daclizumab 150 mg or to a 6-month placebo run-in phase and restart of daclizumab 150 mg; [h] Grouped data including all patients that were randomized to daclizumab 300 mg or to a 6-month placebo run-in phase and restart of daclizumab 300 mg; [i] Excluding skin reactions and autoimmune hepatitis; [j] Cervical carcinoma; [k] Cervical carcinoma; [l] Two cases of cutaneous melanoma; [m] Breast cancer; [n] Breast cancer (three cases), T lymphoma, anal cancer, hypernephroma, pulmonary carcinoid tumor, Hodgkin's lymphoma, cancer of the penis, basal cell carcinoma; [ñ] Endometrial cancer, cutaneous melanoma, metastatic pancreatic carcinoma, squamous cell carcinoma of the skin, cervical cancer, oral squamous cell carcinoma, testicular seminoma, malignant lingual cancer; [o] Basal cell carcinoma, malignant brain tumour, invasive ductal carcinoma of the breast, squamous cell carcinoma of the lip, thyroid cancer, cancer of the uterus; [p] Data not reported in the original work; [q] Ischemic colitis as a local complication of a psoas abscess in a patient recovering from a severe skin rash; [r] Fulminant autoimmune hepatitis developed in a patient randomized to the placebo run-in phase and restart of daclizumab 300 mg; [s] Myocardial infarction, suicide, metastatic pancreatic carcinoma, peritonitis; [t] Aspiration pneumonia; [u] Traumatic subdural haematoma, complications of aspiration pneumonia; [v] Autoimmune thyroid disease, Crohn's disease; [w] Autoimmune thyroid disease, ulcerative colitis, glomerulonephritis; [x] Autoimmune haemolytic anaemia (three cases).

vation and jaundice concomitant with the development of autoimmune thyroiditis. These findings motivated a series of changes in the monitoring measures, so that blood tests of liver function were required prior to each dose, and the concomitant use of some medications associated with hepatotoxicity such as carbamazepine, valproate, lamotrigine, phenytoin, isoniazid, propylthiouracil and nimesulide was limited.

Given that the appearance of these events is unpredictable despite the monitoring plan, profound changes were implemented in the indication of daclizumab in the final report of the EMA, which restrict the use of daclizumab in adult patients with relapsing MS that have responded inadequately to at least two DMT and for which treatment with any other DMT is contraindicated or not adequate, or adult patients with the so-called 'rapidly evolving severe relapsing MS' that cannot be treated with other DMT [59].

Skin reactions

Skin reactions with daclizumab account for one third of the AE and are manifested, in order of frequency, mainly as cutaneous exanthema, dermatitis and eczema. The majority of cases were mild or moderate in intensity.

One study that evaluated the incidence of this type of AE observed this was similar in both the 'high-yield' formulation of subcutaneous daclizumab and the previous formulation (Zenapax). Interestingly, a skin biopsy was performed in those subjects that were treated with Zenapax before changing the high-yield formulation and after one year. In those patients with skin AE, including those with psoriasiform-like lesions, non-specific changes of eczematous dermatitis were observed, but with predominantly CD56+ lymphocytic infiltrates [60].

Of the cutaneous AE related to daclizumab, 37% responded to topical corticosteroids and 27% needed systemic corticosteroids. Four percent of patients treated with daclizumab discontinued treatment due to skin reactions. However, severe cutaneous AE was found in 2% of the patients in the DECIDE study and up to 4% in the follow-up studies. The occurrence of two cases of toxic exanthema with eosinophilia and systemic symptoms (DRESS syndrome) and a case of Stevens-Johnson syndrome have been suspected but could not be confirmed, and may correspond to delayed type IV hypersensitivity reaction phenomena [28,58,61].

It is not uncommon for patients who develop cutaneous AE to have concomitantly or subsequently multiorgan involvement, such as lymphadenopathy or other manifestations of autoimmunity [40,62,63].

Autoimmunity

Apart from autoimmune hepatitis and skin reactions, other AEs of autoimmune nature that affect other organs have been described, including inflammatory bowel disease (non-infectious colitis), thyroiditis, glomerulonephritis, celiac disease, pernicious anaemia, myasthenia gravis, psoriasis, haemolytic anaemia and sarcoidosis [64]. The appearance of an isolated vasculitis of the central nervous system has also been described in a patient receiving daclizumab as off-label therapy after completing a phase II study [65,66].

At the time of review of this article, up to 8 cases of encephalitis (with one death) and noninfectious inflammatory meningoencephalitis have been reported in Europe (seven in Germany and one in Spain), and another three in the United States of America (with two deaths); these cases have led the Biogen and Abbvie laboratories to declare their intention to withdraw the authorisation to commercialize daclizumab [67]. Although these events have not been described in the pivotal trials or in the extension studies, in the CHOICE study, one patient developed a multiorgan syndrome that included brain inflammation [40].

Lymphadenopathy has been described in several of the studies in phases I and II [33], and in the extension phases of the SELECT and DECIDE studies in a proportion that can vary between 1-9% (Table II). Although it is usually mild, in at least one case, lymphadenopathy was caused by systemic sarcoidosis [68].

Neoplasms

No clear relationship has been found between treatment with daclizumab and the appearance of neoplasms. A hypothetical protective effect of the induced expansion of $CD56^{bright}$ NK cells has been described [69], although the rates of onset of neoplasms in MS studies are very similar in the daclizumab group and in the control groups with placebo and with IFNβ1a.

Immune response to vaccination

There is evidence that patients with MS treated with daclizumab develop an immune response to seasonal influenza vaccination as effectively as in healthy volunteers [70,71]. The ability of other vac-

cines to generate an immune response during treatment with daclizumab has not been studied.

Fertility, pregnancy and lactation under daclizumab

Daclizumab is considered within the category C of the FDA for safety in pregnancy. There are no studies that evaluate the effect of daclizumab on human fertility. In animal studies, no toxicity over male or female fertility was observed, nor foetal malformations, although there was an increase in premature abortions. Likewise, the passage of daclizumab through the placenta and its presence in breast milk was verified, as expected for an IgG1 class antibody.

In human studies, exposure to daclizumab has not been associated with an increased risk of preterm birth or specific malformations. To date, only a complex transposition of large vessels has been described in a patient who discontinued daclizumab four months before becoming pregnant and who maintained therapy with IFNβ1a im weekly [72].

Conclusions

The experience of the development of daclizumab has uncovered new pathways and therapeutic targets, by introducing a new mechanism of action through a blockade of a key interleukin in immune regulation and by its effect on a population of cells with immune regulatory capacity as they are NK CD56^{bright} cells.

New drugs are being developed that act on the complex network of cytokines, and there have already been some studies with positive results in MR parameters such as secukinumab, an anti-IL17 [73], but also some failed studies such as ustekinumab, an anti-IL-12/IL-23 also used in psoriasis [74]. A new family of drugs called JAKinibs –from the JAK system (Janus kinases)– that act, not on the extracellular domain of the interleukin receptors, but directly on the second messenger pathways, are being developed for autoimmune diseases such as rheumatoid arthritis (tofacitinib, ruxolitinib, baricitinib) [75].

Undoubtedly, daclizumab has shown superiority in the prevention of relapses against placebo and low-dose IFNβ1a at a level that places it on a par with the rest of current first-line drugs, with a convenient frequency of administration. The effect on the progression of the disease and on neurodegeneration parameters, however, is not clear. On the other hand, it presents safety problems that have meant that the different drug agencies imposed an important restriction on their use. As an example, the NICE guidelines of the United Kingdom in April 2017, even before the second death due to fatal autoimmune hepatitis was acknowledged, limited it to cases of failure or intolerance to two DMTs and in which alemtuzumab were not an option [76]. In this way an anti-intuitive situation was created, in which a therapy with a level of efficacy similar to a first line was relegated as a last option, so it is very possible that the appearance of this drug did not significantly impact on current clinical practice. In any case, although the pharmacovigilance systems have acted quickly, a debate is opened on the bidding of new drugs in MS, especially in those with an unfavourable risk-benefit profile compared to those currently in use.

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Daclizumab en la esclerosis múltiple

Introducción. El daclizumab es un anticuerpo monoclonal dirigido contra la subunidad CD25 del receptor de la interleucina-2, investigado como terapia modificadora de la evolución de la enfermedad en la esclerosis múltiple. La presente revisión aborda cómo se desarrolló el fármaco, cuál es su mecanismo de acción conocido y los datos que se han obtenido hasta la fecha acerca de su eficacia y seguridad.

Desarrollo. El daclizumab ha mostrado superioridad en prevención de brotes frente a placebo e interferón beta-1a de baja dosis en un nivel que lo sitúa a la par del resto de fármacos de primera línea actuales. El efecto sobre la progresión de la enfermedad y sobre parámetros de neurodegeneración, no obstante, no está aclarado. Por otro lado, presenta problemas de seguridad (riesgo de reacciones autoinmunes que incluyen hepatopatía fulminante y encefalitis) que han supuesto finalmente su retirada del mercado. El daclizumab introduce un nuevo mecanismo de acción a través del bloqueo de una interleucina clave en la regulación inmune y por su efecto sobre una población de células con capacidad reguladora, como son las células NK CD56(bright).

Conclusiones. El daclizumab ha demostrado eficacia para frenar el proceso inflamatorio de la esclerosis múltiple, aunque la aparición de efectos secundarios potencialmente graves no ha permitido que su uso impacte de manera significativa en

la práctica clínica actual. El desarrollo de nuevos fármacos en la esclerosis múltiple debe estar supeditado a mantener o mejorar el perfil riesgo-beneficio respecto a los ya en uso.

Palabras clave. Anticuerpo monoclonal. Célula NK. Daclizumab. Esclerosis múltiple. Interleucina 2. Seguridad.