BC-007: Will the „German miracle“ also work for ME/CFS ?

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Abstract

The aptamere BC-007 has shown preliminary promise as a potential pharmaceutical therapy against Long Covid and is currently under investigation in a clinical study. Several questions remain to be answered, among them: How does BC-007 work? How can the apparent remission of several months´ duration after a onetime infusion be explained? And: Can the drug also be effective against Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)?

BC-007 (aka ARC183) is a single-stranded DNA oligonucleotide aptamere originally developed as a thrombin inhibitor in the US and then re-purposed as a broad spectrum neutralizer of G-Protein Coupled Receptor (GPCR) auto-antibodies in cardiomyopathy by a research team around Gerd Wallukat (then at the Max-Delbrück-Centrum for molecular medicine in Berlin/Germany), now working at the German biotech start-up Berlin Cures.[1]–[3]

BC-007 binds to several GPCR auto-antibodies (aabs), to certain antigens (including SARS-CoV-2 antigens) and possibly to other, as of yet undefined, antibodies and/or antigens. Experimental therapy with BC-007 has shown surprisingly positive therapeutic results in a severely affected Long Covid (LC) patient, who has apparently been back to gainful employment and full activity for about 3 months after a one-time infusion therapy.[4] The potential efficacy of BC-007 – which has been reported to be cheap in production as well as well tolerated - has since been confirmed in at least two other LC patients.[5] A controlled clinical trial on LC patients is being planned and could start as early as 2022 after full approval. One of the investigators has stated that they are planning to also do a trial with the drug on ME/CFS patients (here, a timeline has not been offered so far). For details on BC-007, see [4].

It may be of note that other therapies that may possibly work through the removal of aabs have been explored in ME/CFS. A trial of immunoadsorption has reported positive results in some (but not all) patients.[6], [7] Also ME/CFS cases treated with INUSpheresis have been reported, with clinical improvement of the patients treated and an apparent reduction of 50% of the GPCR aab levels measured.[8]

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Mode of action still incompletely understood

As of yet, the exact mode of action of BC-007 is still incompletely understood. A better understanding may also answer the question if this aptamere may be a plausible candidate as a treatment for ME/CFS.

Apparently, the infusion of BC-007 is associated with a rapid drop of certain defined GPCR-aabs, incl. aabs targeting ß2-adrenergic receptors (ß2-AAb), Angiontensin-1 receptor (AT-1-AAb), α1-adrenergic receptor (α1-AAb), MAS receptor (MAS-AAb), and muscarinic2-receptor (M2-AAb). A substantial decrease of aab-levels was already measured 2 hours after the beginning of the infusion, and after 2 days no functional activity was observed for any of the aabs measured; seronegativity then continued throughout the observation period of 4 weeks and beyond. Partial symptom improvement has been reported to start already during the 75-minute infusion but this is based on subjective report only. Vascular perfusion as objectively measured by ocular angiography was improved shortly after the infusion and continued to improve for 1-2 days.[4]

So there are at least two open questions around BC-007:

a) how does the drug work?

b) may it be a candidate for treatment of ME/CFS?

Here I want to comment from my own understanding of the background of LC and ME/CFS.[9]

Most likely mode of action: auto-antibody removal…

For an answer to this question we may need to consider several remarkable features that have been part of the reports of the experimental trials of BC-007. For one, the (subjective) symptomatology in the treated patient apparently starts to partially improve within a very short time period (within an hour, details, see above). Second: the initial (again: subjective) clinical improvement appears to be in step with both changes in certain aab-levels measured and with the improvements in ocular microcirculation as measured by OTC angiography. Third, certain aab levels began to drop during the infusion and remained low/undetectable during the whole observation period (an effect which the inventors of BC-007 had already observed for beta-1 aabs in human experiments with BC-007).[10] Fourth, subjective improvement (including a subjectively full resolution of symptoms in at least one patient) seems to last up to several months. While a relapse has since been recorded in this subjectively fully recovered patient there seems to be ongoing at least partial remission in other patients treated with BC-007.

The congruent timeline of symptom improvement and decrease of GPCR-aabs may suggest that symptom resolution may be causally related to the drop of the specific aab-levels measured. This is also plausible because a similar effect – long lasting persistence of autoantibody absence after a one-time removal - has been observed after immunoadsorption in beta-1-adrenoceptor aab positive transplant candidates with dilated cardiomyopathy.[11]

Autoantibody removal as a mode of action is plausible – but which autoantibodies ?

Apparently, BC-007 removes a host of GPCR-aabs and this may well explain its clinical effect and the measured improvement of cerebral perfusion (OTC angiography assesses the ocular perfusion which

is part of the CNS vasculature). But which one(s) of the aabs removed are responsible for the clinical effect of BC-007? It has been communicated by Berlin Cures that BC-007 may possibly act against a shared domain of GPCR yet to be identified. Therefore, the effect of BC-007 could possibly in part relate to the removal of a wide range of GPCR aabs present but not yet identified in Long Covid. In this respect it is noteworthy that several "novel" GPCR aabs associated with COVID have recently been identified by Cabral-Marquez et al., including against CXCR3, F2R and STAB1 (CXCR3 is important for T-cell and NK-cell signaling, F2R=PAR1 plays a key role in mediating the interplay between coagulation and inflammation, and STAB1 is a transmembrane receptor protein which may function in angiogenesis, lymphocyte homing, cell adhesion, or receptor scavenging.)[12] Also, reactivation of EBV, now understood as a possible pathobiological hallmark of ME/CFS and/or Long COVID, is associated with an extreme upregulation of EBV-induced 2 (EBI2). The latter GPCR has far reaching, pleiotropic effects on immune and CNS-functions[13], [14] and could possibly also included in autoimmune processes affecting the GPCR family. So clearly, as long as the GPCR aab landscape is not fully and systematically explored in Long Covid and ME/CFS it appears premature to postulate a certain mode of action of BC-007 just based on the decline or even disappearance of specific GPCR aabs in response to BC-007 administration.

GPCR-autoantibody removal may not be the only mode of action

However, while GPCR aab removal is a plausible mode of action for BC-007, effects on other (as of yet unidentified) aabs or antigens or other mechanisms may (also) play a role and may need to be considered (again, it needs to be kept in mind that the map of possible autoantigens related to SARS-CoV-2 infection comprises of over hundred auto-antigens, including aabs against ACE-2 and angiotensin II, but also antiphospholipid antibodies, which may or may not be possible targets in any "pheresis" approach). [15]–[17] [18] [19].

As already mentioned, BC-007 also binds to certain SARS-CoV-2 antigens, so its effect could theoretically depend on scavenging SARS-CoV-2 components, including the S1 protein.[20], [21] This may not be a trivial property of the aptamere as there are indications that some of the lingering effects of SARS-CoV-2 may be related to S1 persistence.[22]

However, based on the published data and the apparent rapid improvement of microcirculation measured by OTC angiography, the most likely mode of action of BC-007 may indeed be its ability to scavenge pathologically elevated specific GPCR aabs with vaso-, immune- or neuroactive properties. At least the initial clinical improvement reported may then plausibly be related to increased perfusion in all vascular regions of the body, including in the brain. This assumption would also fit well with older experiments in ME/CFS patients during a head tilt table test in which an infusion of phenylephrine (epinephrine) rapidly improved neurocognitive function.[23] The latter – unfortunately only short lived - effect has been explained through a phenylephrine-triggered loading of the baroreflex with increase in arterial perfusion pressure and decreased hyperventilation and thus better cerebral blood flow and brain function. The assumption of better cerebral blood flow would also fit with a recent case report of rapid improvement of LC symptoms in 2 patients after a one time stellate ganglion block – an effect that the authors also explain by increased brain perfusion.[24]

The hypothesis that BC-007 *directly* improves microcirculation would also fit well with the findings of an indeed dysfunctional cerebral perfusion and/or autoregulation in both LC and ME/CFS patients (as a matter of fact, in ME/CFS this is the most consistent of all findings: ALL ME/CFS patients examined to this avail so far have been shown to have abnormal cerebral perfusion).[25]–[27]

However, BC007 is also an immune modulator and TLR9 inhibitor

There may be even more venues through which BC-007 may achieve its sustained effects, and they also affect the immune/inflammatory matrix of Long Covid:

For one, BC-007 apparently is not only a scavenger of biomolecules, it is also a direct immune modulator. In fact, the inventors of BC-007 consider BC-007 an inhibitor of the toll like receptor 9 (TLR9) and have filed a patent application for this property.[28] TLR9 is an important receptor expressed in immune cells including macrophages and natural killer cells, but also in mast cells and mediates inflammatory responses after both infectious and sterile injury and can in fact be considered a key determinant of the innate immune responses.[29] This involves modulation of inflammatory responses in the CNS. Indeed, TLR9 has been shown to be a key player in neuroinflammation.[30], [31] The receptor has been shown to have a regulatory role in autoimmune diseases, indeed TLR9 antagonists are being developed by the pharmaceutical industry for the treatment of autoimmune diseases. Possibly, and even more of interest to the mode of action of BC-007 may be the fact that TLR9 has been shown to be indispensable in the autoantibody production in B cells in mouse studies.[32]–[34] Also, TLR9 activation seems to be central in initiating and maintaining endothelial inflammation in Covid-19.[35] Therefore, it may be plausible that the inhibiting effect of BC-007 on antibody production may also relate to its effects via TLR9 (here, however, it may again need to be explained why these should persist for months – here again this may hinge on secondary changes like changes in the inflammatory milieu which may drive the clonal expansion of B-cells).

Also, it has to be kept in mind that BC-007 may possibly remove certain inflammatory cytokines. In trials of INUSpheresis, for example, it has been shown that RANTES (CCL5) was removed along with aabs[8] (CCL5 has been suggested as a pivotal cytokine in Long Covid).[36] This may not be a trivial process as pro-inflammatory cytokines are linked to the function of beta-2 receptors in a vicious-cycle dynamic: pro-inflammatory cytokines have been shown to decrease the sensitivity of β-adrenergic receptors; at the same time, chronic activation of β-adrenergic receptors has been shown to induce a pro-inflammatory response with increased expression of TNFα, IL-1β and IL-6 (possibly through NFκB dependent mechanisms).[37] Also, it appears that there is active cross-talk between TNFα receptor signaling and several GPCRs including the β-adrenergic receptor.[37] Therefore, removal of pro-inflammatory cytokines could re-establish normal sensitivity of beta-2 receptors and thus again contribute to the normalization of blood flow (and possibly also reduce sympathetic overdrive and thus decrease further production of inflammatory cytokines).

But how can the lasting effect be explained?

However, this leaves two open questions: How does all this relate to the inflammatory/immune matrix clearly associated with LC (and ME/CFS)? And: how can the long-lasting therapeutic success of a one-time infusion of BC-007 be explained? After all, it is implausible that BC-007 also provides for apoptosis of the aab-producing B-cells – there is just no mechanism to explain this.

More plausibly, the lasting effect of BC-007 may be related to an additional effect on the inflammatory matrix of LC (which may possibly extend to CNS functions):

For one, the improved perfusion could induce a virtuous circle by abolishing the „drivers“ of inflammation like tissue hypoxia and the associated mitochondrial dysfunction, but also by possibly decreasing the disruption of the blood brain barrier (BBB), which has been shown to maintain

neuroinflammation through a constant influx of albumin, fibrinogen and immune cells.[38] The enhanced cerebral perfusion may thus not only cause rapid improvement of brain function through better tissue perfusion but may also abolish the inflammatory milieu which may be at the root of the clonal B-cell expansion and aab-production. The lasting effect of BC-007 may thus reflect the disruption of the vicious circle underlying LC (immune stimulation → inflammation → hypoperfusion → inflammation).

This, however, may not be the only effect through which BC-007 could affect the inflammatory matrix of Long Covid. The adrenergic receptor population, together with a large variety of other GPCRs (including PGE receptors, chemokine receptors, CCR5 or purinergic receptors - which all may potentially also be affected from autoimmune dysfunction after Covid-19), also have profound direct influence on immune processes both in the innate and the adaptive immune system[39], [40] (In fact, dysregulation of β_2-AR in microglia has been shown to contribute to neuroinflammation). Therefore, removal of adrenergic aabs may also have significant reverberations on dysfunctional immune processes, including in the central nervous system.

Here, another property of BC-007 may come into play, namely its ability to inhibit TLR9 (see below). It has been hypothesized by Haberland et al. that the induction of long lasting absence of aabs after a single dose of BC-007 may be due to the fact that BC-007 not only reduces T-cell activation by removing, for instance, beta-1-adrenergic aabs but may also disrupt a vicious cycle needed for aab production by inhibiting TLR9, a co-stimulatory factor stimulating T-cells.[41] Haberland et al. even speculate that with the TLR-9 targeting property of BC-007 “the circle of patients who should benefit from a therapy“ could possibly also include „patients showing symptoms and TLR9 overexpression but no or not yet autoantibodies“ (here, they refer to [42]).

As an alternative (or additional) effect, the improved cerebral perfusion could lead to the abolition of the sympathetic hyperstimulation typical for LongCovid, POTS and ME/CFS. Decreased sympathetic outflow would indeed contribute to normalizing the inflammatory milieu in the brain and in the periphery as sympathetic hyperstimulation has been shown to cause and sustain a pro-inflammatory immune milieu. This hypothesis would again fit well with recent reports of successful treatment of LongCovid by stellate ganglion block which may also work by reducing adrenergic hyperstimulation.[24]

A third plausible mechanism starts from two of the GPCR-aabs scavenged by BC-007, the AT1 and MAS receptor aabs. The AngII/AT1R axis may indeed play a pivotal role in the pathogenesis of LC (and also ME/CFS) and may in part sustain one of the hallmarks of LC and ME/CFS, i.e. the dysregulated cerebral perfusion (with all its consequences). It has been suggested that the cerebral perfusion defect seen in ME/CFS and LC may be related to a blunted baroreflex, which in turn may be a reflection of AT1/MAS receptor dysfunction.[25], [43]–[45] The latter may also be associated with increased angiotensin II levels – as suspected for ME/CFS and proven in Postural Orthostatic Tachycardia Syndrome (POTS).[46], [47] The increased angiotensin II levels in turn may go along with sympathetic stimulation through epinephrine release, reduced blood flow to the brain, oxidative stress, but also with regulatory CNS dysfunctions, blood brain barrier dysfunction, and, possibly, neuroinflammation – all features that have been implicated in the pathogenesis of LC and ME/CFS.[48]–[50] In this hypothetical explanation of the mode of action of BC-007, this aptamere would restore a functioning AngII/AT1R axis by scavenging AT1/MAS aabs, and thus restore the baroreflex and cerebral autoregulation/perfusion to full function. (To pursue this hypothesis further, it would be interesting to measure angiotensin II and its precursors during and after infusion of BC-007).

Here it may also be important to understand that the AngII/AT1R axis is an important regulatory circuit within the brain („b-RAS“) which is directly and indirectly involved in autonomous and cardiovascular regulation, vigilance and immune signalling (indeed, Ang II also serves as a neurotransmitter). Any effects of BC-007 on AT1/MAS receptor function may therefore have profound reverberations on CNS function which may in part be independent of effects on the microcirculation.

The same argument may apply to another GPCR possibly rendered dysfunctional by aabs in Long Covid (and ME/CFS), namely the endothelin 1 (ET1) B receptor group which has also been shown to have regulatory functions spanning the microcirculation *and* CNS regulation.[51]

Also, it needs to be kept in mind that a large part of GPCR aabs may have direct effects on CNS regulation. For instance, the majority of adrenergic receptors are expressed in the brain (especially in the brain regions involved in autonomic activity and regulation); indeed, muscarinergic and adrenergic receptors span a wide range of effector and regulatory functions in the brain, including memory, attention, motor control, sleep-wake-regulation but also memory and cognition. So it may be premature to relate the effects of the removal of adrenergic aabs to effects on the vasculature and/or the imune system *alone*. (Here, of course, it may be argued that aabs do not readily cross the BBB. However, this a) does not preclude autoimmunity to happen within the CNS / the innate immune system of the brain and b) this may not apply to an inflammatory CNS milieu, in which the blood-brain barrier is partially dysfunctional. Also, some areas of the CNS are normally devoid of a BBB, such as the circumventricular organs mediating communication between the hypothalamus and brainstem.

In summary, BC-007 may achieve its long lasting effect not only be normalizing blood flow in general but also by abolishing drivers of inflammation (including neuroinflammation) and adrenergic hyperstimulation as well as exerting effects on the immune system and regulatory CNS functions.

Could BC-007 be effective for ME/CFS?

BC-007 appears as a drug with pleiotropic activities. It is a scavenger of biomolecules, which may have significant direct effects on vascular, immune, and possibly CNS function. BC-007 additionally may have immune-modulatory properties and have indirect effects on the immune system. A broad mixture indeed: BC-007 may have microcirculatory , immune-modulatory and anti-inflammatory properties (not to forget the anti-coagulation effect for which the aptamere was originally developed).

What does all this mean for ME/CFS? If a similar constellation of aabs is to be found in ME/CFS as in the Long Covid patients treated with BC-007 so far, the patients may benefit from BC-007 to some – as of yet unforeseeable - extent (which may range from small to large improvements, and from one-time, several to regularly repeated infusions). It has indeed been assumed that similar aabs as found in LongCovid are to be found in about a third of ME/CFS patients (this ratio may actually be higher as the bioassay used by Berlin Cures may be more sensitive than the ELISA used in former studies). The same would apply to POTS in which a similar set of aabs has been recognized as part of the pathophysological matrix.

It also needs to be recognized that the role of the GPCR aab networks is far from being completely understood. For one, certain aabs in certain concentrations may be part of the normal regulatory immune matrix. Some of these “normal” autoantibodies may even be protective (anti ATR1 aabs, for instance, are preliminarily suggested to be protective against severe COVD 19).[52] Also, it has not

yet been systematically investigated if and how GPCR aabs in Long Covid or ME/CFS correlate with disease severity nor in which range the levels may fluctuate intraindividually between good days and bad days (i.e. during PEM). Also, it still needs to be assessed which GPCR aabs exactly correlate with clinical or biophysiological measurements (like retinal perfusion – which could be a marker for cerebral blood flow and thus a meaningful research tool, some open questions about intraindividual variance between good days and periods of PEM notwithstanding).

Could BC-007 even work for patients without elevated GPCR aabs? Clearly, this is speculative but, as noted earlier and suggested by the inventors of BC-007, may be plausible based on the possible action of BC-007 via TLR9 suppression (for details, see above). [41]

As always, it will all come down to further research, which has now started with the disCOVer and the reCOVer studies at the University of Erlangen.

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