IMMUNO DEFICIENCY UK

Special Edition Newsletter

Understanding active and passive immunity

Updates on the latest developments in passive immunity to prevent and treat COVID-19 disease

The body has several lines of defence against attacks from tiny organisms (micro-organisms) such as bacteria, viruses, parasites or fungi. These organisms can cause diseases and are called 'pathogens'. Pathogens include some proteins or sugars on their surface on which the body's antibodies attach. These proteins or sugars are also known as **antigens**.

Immunity is the body's ability to resist a particular infection caused by a pathogen. The body's immunity consists of:

- **'Innate immunity'** (also known as **'genetic'** or **'family' immunity**): it is a type of natural protection against disease that is inherited or based on genetic predisposition. This type of immunity confers protection from birth until death
- **'Acquired immunity'** (also known as **'adaptive immunity'**): it is the protection against specific pathogens that develops after exposure to them

If we now focus more specifically on **acquired immunity**, it may be either **natural** or **artificial** and both of these types have **active and passive elements.**

Active Immunity

Active immunity is the process the body uses to fight pathogens and it develops from the **direct exposure** to a pathogen (virus, bacterium, etc.).

A good example of **'natural active immunity'** is the natural defence put in place by the body to fight a cold.

On the other hand, **'artificial active**

immunity' is protection to a disease through vaccination (immunisation) such as the flu vaccine, the measles mumps rubella (MMR) vaccine or the COVID-19 vaccine.

Active immunity is also involved in **autoimmune diseases** (when the body's defences attack its own cells) and **allergic reactions**. An allergic reaction is a specific type of immune response to an antigen of the sort usually associated with parasite infections. The same response can occur to similar proteins seen in the plant and animal world, when these immune reactions occur to harmless proteins in our food or environment they are known as allergic reactions. The most extreme form of allergic reactions is called anaphylaxis.

Different types of cells are involved in natural active immunity:

- T cells (cytotoxic T cells and helper T cells)
- B cells (memory B cells and plasma B cells)
- Antigen-presenting cells (dendritic cells and macrophages)

Active immunity takes some time to build after the body is exposed to an antigen for the first time. That initial reaction is called the **'primary response'**. The **'secondary response'**, when the body is re-exposed to the same antigen, is much quicker and more specific.

Active immunity can **last many years** or even an **individual's whole life** thanks to the production of immune memory cells. It is worth noting that this only applies to individuals with normally functioning immune systems as active immunity does not work fully in patients with many immunodeficiencies.

Passive Immunity

Passive immunity is the protection acquired by an individual through the introduction of antibodies into the body by **external** means.

For instance, a **foetus** acquires antibodies through the **placenta** of its mother. A **breast-fed baby** is protected against some infections thanks to its mother's antibodies present in breastmilk (colostrum).

Patients with primary immunodeficiencies receive immunoglobulin treatments which are medicines containing antibodies to fight off pathogens.

These immunoglobulins come from the liquid component of blood (plasma) of other individuals after extensive, sophisticated and stringent processing to ensure safety.

Another example of passive immunity is the protection offered by a **snake antivenom** following a bite.

Passive immunity is not triggered by the exposure to an antigen and it does not involve the body's own production of antibodies.

Unlike active immunity, there is **no delay in response** to protection from passive immunity; its action is immediate.

Duration of action is another major difference when comparing passive and active immunity. In passive immunity, there is no **immunological memory**, contrary to active immunity. This means that the duration of passive immunity is much shorter: only a few days or a few weeks, which is why immunoglobulin infusions, for instance, must take place at regular intervals (these will vary from one individual to another).

Topical examples of passive immunity: convalescent plasma and monoclonal antibody therapies in COVID-19

A very topical example of **passive immunity** is the use of **convalescent plasma** from patients who have recovered from COVID-19 infection and **monoclonal antibodies** with high levels of activity against the virus (neutralising antiviral activity).

These emerging approaches have the potential to be used for **both therapy and prevention** of COVID-19 infections.

Convalescent plasma

Plasma (the liquid component of blood that holds the blood cells of whole blood in suspension and carries cells and proteins throughout the body) should theoretically contain high levels of antibodies against viruses.

Therefore, the objective of infusing convalescent plasma inpatients with COVID-19 is to **help accelerate their recovery** and this approach has been used during other pandemics (e.g. 1918 Spanish flu, 2014 Ebola epidemic in west Africa, etc.).

Several **studies** have been conducted in the use of convalescent plasma in patients infected with the SARS-CoV2 virus responsible for COVID-19 disease. Results are now emerging from studies in **India** (relatively small study, the 'PLACID' trial, with 464 adult patients hospitalised with COVID-19), the **UK** (large-scale, 'RECOVERY' trial, with tens of thousands of patients hospitalised with COVID-19) and the USA (the 'COVID-19 Convalescent Plasma Expanded-Access Program' initiated by the Mayo Clinic including over 3,000 patients hospitalised with COVID-19), amongst others. Overall, the studies suggested that more work needed to be conducted to validate this treatment approach, to help standardise it and target it at those for whom it would be most beneficial.

In the US study, it was found that less severely ill patients who had received a plasma infusion with high levels of anti-COVID-19 antibodies were less likely to die (22.3%) than those who had received an infusion with a lower level of antibodies (29.6%). However, it was also noted that convalescent plasma did not provide any benefits for more seriously ill patients who required ventilation.

There are some **limitations and concerns** associated with the use of convalescent plasma:

- Quantitatively, this approach is dependent on receiving **enough plasma donations** from patients who have recovered from COVID-19
- Qualitatively, these patients need to have had a **good and long-lasting immune response** to the SARS-CoV2 virus and **high levels of antibodies**
- **The duration of immunity** and the **levels of antibodies** required to remain protected against infection are also still unclear
- Convalescent plasma is **very difficult to standardise** due to the variation of immune response from one individual to another, which means there may be variability between batches
- Because plasma is a blood product, **blood type matching is required**, as well as stringent **screening** for pathogens carried by blood such as hepatitis viruses, HIV and parasites
- The **timing** of this treatment is likely to be critical: if given at the wrong time to a patient, it could either be **ineffective** or **dangerous**, as it can enhance or induce an exaggerated inflammatory response which can sometimes lead to organ failure and death (this group of related medical conditions in which the immune system produces too many inflammatory signal is called a 'cytokinestorm syndrome')

Monoclonal antibodies

Monoclonal antibodies offer a novel approach to the **prevention and the treatment** of COVID-19 infections, especially in **patients at increased risk of severe disease**. They are currently undergoing clinical trials; initial results have been published and the Food and Drug Administration (FDA) in the US has granted **emergency use authorisations** for some of **these medicines**.

Monoclonal antibodies come from duplicates (clones) of a single 'parent' immune cell (B cell, in this case) or are produced artificially in a laboratory through genetic engineering. This cell recognises and reacts to a specific region of an antigen.

In COVID-19, monoclonal antibodies target **specific** neutralising sites on the **spike protein** of the SARS-CoV2 virus. Spike protein is how the virus enters the body's cells.

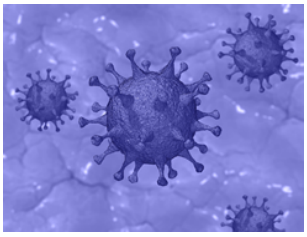

Illustration of the SARS-CoV2 virus

Credit: Pete Linforth (Pixabay.com)

Thanks to current technologies, monoclonal antibodies can be produced safely, quickly and on a large scale.

The side effects of some convalescent plasma antibodies, which are less specific and have the potential to contribute to tissue damage, are less likely to happen with the use of **single or combinations** of monoclonal antibodies. These combinations are also sometimes referred to as **'monoclonal antibody cocktails'**.

There are currently **three types of monoclonal antibodies** undergoing clinical trials:

- **Single** monoclonal antibody: **bamlanivimab** (Eli Lilly)
- **Cocktail** of two monoclonal antibodies: **casirivimab** and **imdevimab**, also known as 'REGN-COV2' (Regeneron), given as a single intravenous (IV) injection
- **Cocktail** of two monoclonal antibodies: **bamlanivimab** and **etesevimab** (Eli Lilly)

The use of single monoclonals has been implicated with the development of “escape variants” and the combinations of monoclonals or cocktails make this less likely.

The FDA in the US granted **emergency use authorisation (EUA)** for Eli Lilly’s bamlanivimab and Regeneron’s casirivimab-imdevimab combination in **November 2020**, in outpatients (adults and children aged 12 years and older) with mild-to-moderate COVID-19 and at high risk of severe disease. These authorisations were based on **interim** analyses of two **outpatient**, phase II, randomised controlled trials which showed **a reduction in COVID-19-related hospitalisations or accident and emergency (A&E) visits**.

On 21st January 2021, Eli Lilly announced that in its phase III, **‘BLAZE-2’, COVID-19 prevention study, Bamlanivimab** significantly **reduced the risk of contracting symptomatic** COVID-19 among **residents and staff of long-term care facilities.**

A few days later, the same company published data from its **‘BLAZE-1’** phase III clinical trial which included 1,035 outpatients with **mild-to-moderate COVID-19 and at risk of progression to severe** disease, demonstrating that treatment with the **bamlanivimab-etesevimab combination** resulted in a statistically significant **risk reduction of 70% in hospitalisations or deaths** (p=0.0004).

This press release led to the **FDA’s emergency use authorisation** of the **bamlanivimab-etesevimab combination**, in February 2021, for the treatment of mild-to-moderate COVID-19 disease in patients at high risk of progression to severe disease.

Immediately after Eli Lilly’s data release on its combination treatment, **Regeneron announced positive interim results** from an ongoing phase III study evaluating its monoclonal antibody cocktail **REGN-COV2** as a ‘**passive vaccine**’ for **preventing COVID-19 in people at high risk of infection** due to household exposure to a patient with SARS-CoV-2. The data suggested Regeneron’s combination **may reduce transmission** of the virus, the **viral load** and the **disease burden** in individuals who still did get infected.

Early February 2021, it was announced that the **European Medical Agency (EMA)** had started reviewing the preliminary study results of **Regeneron’s** monoclonal antibody cocktail **REGN-COV2** for the **treatment and prevention** of COVID-19.

Overall these **initial results** are **promising** as they show that monoclonal antibody cocktails may help prevent COVID-19 disease in high-risk individuals. However, the high treatment cost may imply a limited use for this purpose.

Nonetheless, these results may suggest **that monoclonal antibodies and convalescent plasma** could potentially help protect patients with immunodeficiencies, in whom a COVID-19 vaccine has limited or no effectiveness. **Further research is necessary and ongoing** with these emerging medicines to help determine their efficacy and safety, as well as their place for the prevention and treatment of COVID-19 disease including identifying the best suitable patient populations.

Glossary of terms

antigen – any foreign substance that provokes an immune response when introduced into the body.

autoimmune/autoimmunity – when an individual's immune system attacks the body's own tissues or vessels.

B-cell – a type of white blood cell (lymphocyte) that produces antibodies.

convalescent plasma – plasma from people who have recovered from an infection.

cytotoxic T cells – a type of T cell that can destroy virus-infected cells and cancer cells.

dendritic cells – white blood cells that process foreign substances (antigens) and put it on their surface. There the antigen interacts with other cells of the immune system to activate specific responses.

helper T cell – a sub-set of T-cells that help B-cells and T-cells to function better.

immunological memory – the ability of the immune system to respond more rapidly and effectively to pathogens that have been encountered previously.

macrophage – a type of immune cell found in the tissues, able to destroy invading bacteria or other foreign material.

memory B cells – a type of B cell that remain in the body after an infection and retain a memory of the foreign substance (antigen) that caused the infection.

monoclonal antibody – identical copies of one type of antibody.

neutralising antiviral activity – neutralisation of the virus that makes it no longer infectious or pathogenic.

passive immunity – the administration of antibodies to an unimmunised person to provide temporary protection against a microbial agent or toxin.

plasma B cell – a specific subtype of B-cell that is found within the bone marrow or lymph nodes. Plasma cells are responsible for most high-quality antibody production.

T cell – a type of white blood cell (lymphocyte) that helps the immune system work properly to fight infection.

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