Glucocorticoids (GC) are potent anti-inflammatory and immunosuppressive drugs which are used successfully to treat many disorders, including rheumatoid arthritis, polymyalgia rheumatica, giant cell arteritis, myositis, systemic lupus erythematoses and other rheumatic diseases. However, these drugs also have the potential to cause severe adverse effects, particularly if high doses are used for prolonged periods. Therefore, the benefits of GC therapy must be balanced against the potential risks. Key strategies to achieve this goal include following guideline recommendations regarding GC therapy dosing, monitoring for potential adverse events, and adverse event prevention and management, using or developing new therapeutic advances to improve the therapeutic balance. This talk briefly mentions a recent publication discussing the question under which conditions long-term treatment with GC has an acceptably low level of harm, but focuses then on two current approaches to minimise GC adverse effects while keeping or even enhancing their anti-inflammatory efficacy, namely the development of dissociated agonists of the GC receptor (DAGR) and liposomal GC. In order to do so, a deep understanding of both the genomic and non-genomic mechanisms of glucocorticoid actions is needed. Therefore, this underlying basic science will be thoroughly discussed in this talk.

In brief: first, GC primarily act via the classical genomic pathway, which is mediated by the cytosolic GC receptor (cGR). To this end, GC pass the plasma membrane and bind to its receptor which exists as a multi-protein complex in the cytoplasm. After activation, the GC-cGR complex is translocated into the nucleus and binds as a homodimer to DNA-binding sites. As a result, transcription and translation of anti-inflammatory and regulator proteins is induced. This process is termed transactivation. Apart from this, the activated GC-cGR complex can also inhibit the synthesis of proinflammatory mediators by direct or indirect interaction with essential transcription factors or by competition for nuclear coactivators which is termed transrepression. Although currently being discussed somewhat controversially, transrepression is hypothesised as primarily mediating the unwanted anti-inflammatory effects while transactivation is held to be responsible for the major number of adverse effects. This drives the development of DAGR. Secondly, GCs also act via several different rapid non-genomic mechanisms. These mechanisms contribute to therapeutic effects induced with very high dosages (e.g. pulse therapy), and are thought to mediate - at least in part - the beneficial effects seen with liposomal GCs.

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